=> fil reg; d ide l19; d ide l20; d ide l21; d ide l24; d ide l26
FILE 'REGISTRY' ENTERED AT 16:36:12 ON 30 MAY 2003

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 29 MAY 2003 HIGHEST RN 522590-15-4
DICTIONARY FILE UPDATES: 29 MAY 2003 HIGHEST RN 522590-15-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

L19 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **593-77-1** REGISTRY
CN Methanamine, N-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Hydroxylamine, N-methyl- (6CI, 7CI, 8CI)
OTHER NAMES:
CN .beta.-Methylhydroxylamine
CN Methylhydroxylamine
CN N-Hydroxymethanamine
CN N-Hydroxymethylamine
CN N-Methylhydroxyamine
CN N-Methylhydroxylamine
FS 3D CONCORD
MF C H5 N O
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, NIOSHTIC, RTECS*, SYNTHLINE, TOXCENTER, USPATFULL, VTB
(*File contains numerically searchable property data)

$H_3C-NH-OH$

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

557 REFERENCES IN FILE CA (1957 TO DATE)
16 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
557 REFERENCES IN FILE CAPLUS (1957 TO DATE)
24 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L20 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS

RN 622-30-0 REGISTRY
CN Benzenemethanamine, N-hydroxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Hydroxylamine, N-benzyl- (6CI, 7CI, 8CI)
OTHER NAMES:
CN Benzylhydroxylamine
CN N-Benzylhydroxylamine
CN N-Hydroxybenzylamine
CN O-Benzylhydroxyamine
FS 3D CONCORD
DR 159879-46-6
MF C7 H9 N O
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, NIOSHTIC, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

HO—NH—CH_2—Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

309 REFERENCES IN FILE CA (1957 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
310 REFERENCES IN FILE CAPLUS (1957 TO DATE)
15 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L21 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 16649-50-6 REGISTRY
CN 2-Propanamine, N-hydroxy-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Hydroxylamine, N-tert-butyl- (6CI, 8CI)
OTHER NAMES:
CN 2-Hydroxylamino-2-methylpropane
CN N-Hydroxy-tert-butylamine
CN N-t-Butylhydroxylamine
CN N-tert-Butylhydroxylamine
CN tert-Butylhydroxylamine
FS 3D CONCORD
MF C4 H11 N O
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMINFORMRX, IFICDB, IFIPAT, IFIUDB, MEDLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

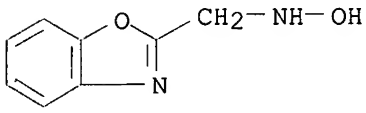
HO—NH—Bu-t

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

181 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
181 REFERENCES IN FILE CAPLUS (1957 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

Searched by Barb O'Bryen, STIC 308-4291

L24 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **337905-21-2** REGISTRY
CN 2-Benzoxazolemethanamine, N-hydroxy- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C8 H8 N2 O2**
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L26 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **5080-24-0** REGISTRY
CN **1-Butanamine, N-hydroxy- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Hydroxylamine, N-butyl- (6CI, 7CI, 8CI)
OTHER NAMES:
CN Butylhydroxylamine
CN N-Butylhydroxylamine
FS 3D CONCORD
DR 159879-54-6
MF **C4 H11 N O**
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMINFORMRX, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

HO—NH—Bu-n

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

33 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
33 REFERENCES IN FILE CAPLUS (1957 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> fil capl; d que l15; d que l16;d que l17; d que l18

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FILE COVERS 1907 - 30 May 2003 VOL 138 ISS 23
FILE LAST UPDATED: 29 May 2003 (20030529/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
L9          7584 SEA FILE=CAPLUS ABB=ON  (CELL? OR REPLICATIVE)(3A)(AGING OR
                 SENESCENCE)/OBI
L10        23516 SEA FILE=CAPLUS ABB=ON  OXIDATIVE(2A)(STRESS? OR DAMAG?)/OBI
L11        20136 SEA FILE=CAPLUS ABB=ON  HYDROXYLAMINE#/OBI
L12           87 SEA FILE=CAPLUS ABB=ON  AMINES/CT(L)HYDROXYL
L13           23 SEA FILE=CAPLUS ABB=ON  (L9 OR L10) AND (L11 OR L12)
L14       236045 SEA FILE=CAPLUS ABB=ON  SCREEN?
L15            1 SEA FILE=CAPLUS ABB=ON  L13 AND L14
```

```
L9          7584 SEA FILE=CAPLUS ABB=ON  (CELL? OR REPLICATIVE)(3A)(AGING OR
                 SENESCENCE)/OBI
L10        23516 SEA FILE=CAPLUS ABB=ON  OXIDATIVE(2A)(STRESS? OR DAMAG?)/OBI
L11        20136 SEA FILE=CAPLUS ABB=ON  HYDROXYLAMINE#/OBI
L12           87 SEA FILE=CAPLUS ABB=ON  AMINES/CT(L)HYDROXYL
L13           23 SEA FILE=CAPLUS ABB=ON  (L9 OR L10) AND (L11 OR L12)
L16            2 SEA FILE=CAPLUS ABB=ON  DRUG/CW AND L13
```

```
L9          7584 SEA FILE=CAPLUS ABB=ON  (CELL? OR REPLICATIVE)(3A)(AGING OR
                 SENESCENCE)/OBI
L10        23516 SEA FILE=CAPLUS ABB=ON  OXIDATIVE(2A)(STRESS? OR DAMAG?)/OBI
L11        20136 SEA FILE=CAPLUS ABB=ON  HYDROXYLAMINE#/OBI
L12           87 SEA FILE=CAPLUS ABB=ON  AMINES/CT(L)HYDROXYL
L13           23 SEA FILE=CAPLUS ABB=ON  (L9 OR L10) AND (L11 OR L12)
L17            6 SEA FILE=CAPLUS ABB=ON  PHARMAC?/SC,SX AND L13
```

```
L9          7584 SEA FILE=CAPLUS ABB=ON  (CELL? OR REPLICATIVE)(3A)(AGING OR
                 SENESCENCE)/OBI
L10        23516 SEA FILE=CAPLUS ABB=ON  OXIDATIVE(2A)(STRESS? OR DAMAG?)/OBI
L11        20136 SEA FILE=CAPLUS ABB=ON  HYDROXYLAMINE#/OBI
L12           87 SEA FILE=CAPLUS ABB=ON  AMINES/CT(L)HYDROXYL
L13           23 SEA FILE=CAPLUS ABB=ON  (L9 OR L10) AND (L11 OR L12)
L18            3 SEA FILE=CAPLUS ABB=ON  9/SC,SX AND L13
```

Section code - Biochemical methods

```
=> s l15 or l16 or l17 or l18

L110           8 L15 OR L16 OR L17 OR L18
```

```
=> fil medl; d que l59

FILE 'MEDLINE' ENTERED AT 16:36:17 ON 30 MAY 2003

 FILE LAST UPDATED: 29 MAY 2003 (20030529/UP). FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L40       16714 SEA FILE=MEDLINE ABB=ON  HYDROXYLAMINES+NT/CT
L41       73602 SEA FILE=MEDLINE ABB=ON  DRUG EVALUATION, PRECLINICAL+NT/CT
L43        6846 SEA FILE=MEDLINE ABB=ON  CELL AGING+NT/CT
L45       13449 SEA FILE=MEDLINE ABB=ON  OXIDATIVE STRESS/CT
L58       23548 SEA FILE=MEDLINE ABB=ON  ANTIOXIDANTS/CT
L59           0 SEA FILE=MEDLINE ABB=ON  L40 AND L41 AND (L43 OR L45 OR L58)


=> fil embase; d que l91; d que l96; d que l94

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 FILE COVERS 1974 TO 29 May 2003 (20030529/ED)

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 substance identification.


L85        3715 SEA FILE=EMBASE ABB=ON  HYDROXYLAMINE+NT/CT
L86        2631 SEA FILE=EMBASE ABB=ON  CELL AGING/CT OR "CELL AGING, CELL
                DEGENERATION AND CELL SURVIVAL"/CT
L87       23619 SEA FILE=EMBASE ABB=ON  OXIDATIVE STRESS/CT
L88          48 SEA FILE=EMBASE ABB=ON  L85 AND (L86 OR L87)
L89        9083 SEA FILE=EMBASE ABB=ON  CELL PROTECTION/CT
L90       11148 SEA FILE=EMBASE ABB=ON  ANTIOXIDANT ACTIVITY/CT
L91           9 SEA FILE=EMBASE ABB=ON  L88 AND (L89 OR L90)


L85        3715 SEA FILE=EMBASE ABB=ON  HYDROXYLAMINE+NT/CT
L92       62888 SEA FILE=EMBASE ABB=ON  DRUG SCREENING/CT
L95      224106 SEA FILE=EMBASE ABB=ON  CELL CULTURE+NT/CT
L96           4 SEA FILE=EMBASE ABB=ON  L85 AND L95 AND L92


L85        3715 SEA FILE=EMBASE ABB=ON  HYDROXYLAMINE+NT/CT
L86        2631 SEA FILE=EMBASE ABB=ON  CELL AGING/CT OR "CELL AGING, CELL
                DEGENERATION AND CELL SURVIVAL"/CT
L87       23619 SEA FILE=EMBASE ABB=ON  OXIDATIVE STRESS/CT
L89        9083 SEA FILE=EMBASE ABB=ON  CELL PROTECTION/CT
L90       11148 SEA FILE=EMBASE ABB=ON  ANTIOXIDANT ACTIVITY/CT
L92       62888 SEA FILE=EMBASE ABB=ON  DRUG SCREENING/CT
```

```
L94          1 SEA FILE=EMBASE ABB=ON  L85 AND L92 AND (L86 OR L87 OR L89 OR
                L90)


=> s l91 or l96 or l94

L111        14 L91 OR L96 OR L94

=> fil wpids; d que l72; d que l76

FILE 'WPIDS' ENTERED AT 16:36:18 ON 30 MAY 2003
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FILE LAST UPDATED:          29 MAY 2003      <20030529/UP>
MOST RECENT DERWENT UPDATE:     200334        <200334/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS  <<<

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    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

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 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L66        5304 SEA FILE=WPIDS ABB=ON  HYDROXYLAMINE# OR HYDROXYL AMINE#
L67         750 SEA FILE=WPIDS ABB=ON  OXIDATIVE?(2A)(DAMAG? OR STRESS?)
L68        1186 SEA FILE=WPIDS ABB=ON  (CELL? OR REPLICATIVE)(3A)(AGING OR
                SENESCENCE OR SURVIVAL)
L71      167168 SEA FILE=WPIDS ABB=ON  PRIMARY
L72           1 SEA FILE=WPIDS ABB=ON  L66 AND (L67 OR L68) AND L71



L66        5304 SEA FILE=WPIDS ABB=ON  HYDROXYLAMINE# OR HYDROXYL AMINE#
L69      223506 SEA FILE=WPIDS ABB=ON  SCREEN?
L75        9273 SEA FILE=WPIDS ABB=ON  L69(5A)(DRUG# OR PHARMACEUT? OR
                COMPOUND# OR THERAP?)
L76           8 SEA FILE=WPIDS ABB=ON  L66 AND L75


=> s l72 or l76

L112        9 L72 OR L76

=> fil DRUGU, BIOTECHNO, CABA, IPA, BIOSIS, TOXCENTER, ANABSTR

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```
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FILE 'ANABSTR' ENTERED AT 16:36:20 ON 30 MAY 2003
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=> d que l109

L100      134424 SEA (CELL? OR REPLICATIVE)(3A)(AGING OR SENESCENCE OR SURVIVAL
                 OR PROTECT?)
L101       88900 SEA OXIDATIVE?(2A)(STRESS? OR DAMAG?)
L102      137290 SEA ANTIOXIDANT#
L103      229308 SEA (SCREEN? OR EVALUAT? OR TEST?)(3A)(DRUG# OR PHARMACEUT? OR
                 COMPOUND# OR THERAP?)
L107       17787 SEA HYDROXYLAMINE# OR HYDROXYL AMINE#
L109          21 SEA L107 AND L103 AND (L100 OR L101 OR L102)


=> dup rem l110,l111,l109,l112
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PROCESSING COMPLETED FOR L110
PROCESSING COMPLETED FOR L111
PROCESSING COMPLETED FOR L109
PROCESSING COMPLETED FOR L112
L113          42 DUP REM L110 L111 L109 L112 (10 DUPLICATES REMOVED)
                 ANSWERS '1-8' FROM FILE CAPLUS
                 ANSWERS '9-21' FROM FILE EMBASE
                 ANSWERS '22-25' FROM FILE DRUGU
                 ANSWER '26' FROM FILE BIOTECHNO
                 ANSWER '27' FROM FILE BIOSIS
                 ANSWERS '28-34' FROM FILE TOXCENTER
                 ANSWERS '35-42' FROM FILE WPIDS

=> d ibib ab 1-42
```

L113 ANSWER 1 OF 42 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:806974 CAPLUS
TITLE: Differential protection by nitroxides and **hydroxylamines** to radiation-induced and metal ion-catalyzed **oxidative damage**
AUTHOR(S): Xavier, Sandhya; Yamada, Ken-ichi; Samuni, Ayelet M.; Samuni, Amram; DeGraff, William; Krishna, Murali C.; Mitchell, James B.
CORPORATE SOURCE: Radiation Biology Branch, National Cancer Institute, Bethesda, MD, 20892-1002, USA
SOURCE: Biochimica et Biophysica Acta (2002), 1573(2), 109-120
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Modulation of radiation- and metal ion-catalyzed oxidative-induced damage using plasmid DNA, genomic DNA, and cell survival, by three nitroxides and their corresponding hydroxylamines, were examd. The antioxidant property of each compd. was independently detd. by reacting supercoiled DNA with copper II/1,10-phenanthroline complex fueled by the products of hypoxanthine/xanthine oxidase (HX/XO) and noting the protective effect as assessed by agarose gel electrophoresis. The nitroxides and their corresponding hydroxylamines protected approx. to the same degree (33-47% relaxed form) when compared to 76.7% relaxed form in the absence of protectors. Likewise, protection by both the nitroxide and corresponding hydroxylamine were obsd. for Chinese hamster V79 cells exposed to hydrogen peroxide. In contrast, when plasmid DNA damage was induced by ionizing radiation (100 Gy), only nitroxides (10 mM) provide protection (32.4-38.5% relaxed form) when compared to radiation alone or in the presence of hydroxylamines (10 mM) (79.8% relaxed form). Nitroxide protection was concn. dependent. Radiation cell survival studies and DNA double-strand break (DBS) assessment (pulse field electrophoresis) showed that only the nitroxide protected or prevented damage, resp. Collectively, the results show that nitroxides and hydroxylamines protect equally against the damage mediated by oxidants generated by the metal ion-catalyzed Haber-Weiss reaction, but only nitroxides protect against radiation damage, suggesting that nitroxides may more readily react with intermediate radical species produced by radiation than hydroxylamines.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L113 ANSWER 2 OF 42 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
ACCESSION NUMBER: 2001:320074 CAPLUS
DOCUMENT NUMBER: 134:344595
TITLE: Pharmaceutical compositions comprising primary N-**hydroxylamines**
INVENTOR(S): Ames, Bruce N.; Atamna, Hani
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030979	A1	20010503	WO 2000-US29634	20001027
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6455589	B1	20020924	US 1999-429412	19991028

PRIORITY APPLN. INFO.: US 1999-429412 A 19991028

Searched by Barb O'Bryen, STIC 308-4291

OTHER SOURCE(S): MARPAT 134:344595

AB The invention provides pharmaceutical compns. comprising primary N-hydroxylamines and related therapeutic, prophylactic, diagnostic and screening methods. The pharmaceutical compns. generally comprise a pharmaceutical compn. comprising an orally administrable effective unit solid dosage of a primary N-hydroxylamine or a pharmaceutically acceptable salt thereof and substantially free of a nitrone corresponding to the hydroxylamine. The compns. are useful for reducing oxidative damage or delaying senescence. N-tert-butylhydroxylamine, a hydrolysis product of .alpha.-phenyl-N-tert-butylnitrone, delayed senescence in IMR90 human lung fibroblasts. Tablets, capsules, and other formulations of N-tert-butylhydroxylamine are given.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L113 ANSWER 3 OF 42 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:435928 CAPLUS

DOCUMENT NUMBER: 137:151924

TITLE: Noninvasive diagnostic tool for inflammation-induced **oxidative stress** using electron spin resonance spectroscopy and an extracellular cyclic **hydroxylamine**

AUTHOR(S): Dikalov, Sergey I.; Dikalova, Anna E.; Mason, Ronald P.

CORPORATE SOURCE: Laboratory of Pharmacology and Chemistry, National Institutes of Health, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709, USA

SOURCE: Archives of Biochemistry and Biophysics (2002), 402(2), 218-226
CODEN: ABBIA4; ISSN: 0003-9861

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Inflammation is one of the leading causes of the many pathol. states assocd. with oxidative stress. A crucial role in the development of inflammation-induced oxidative stress is played by reactive oxidant species (ROS), which are very difficult to detect in vivo. One of the most sensitive and definitive methods in the detection of ROS is ESR, esp. as used in conjunction with spin trapping. Unfortunately, the commonly used nitrone spin traps have a very low efficacy for trapping superoxide radicals, and their radical adducts are not stable. To address this deficiency, we have developed neg. charged cyclic hydroxylamines such as 1-hydroxy-4-phosphonooxy-2,2,6,6-tetramethylpiperidine (PP-H) for the detection of reactive oxidant species as a diagnostic tool for extracellular inflammation-induced oxidative stress. We used inflammation induced by a bacterial endotoxin lipopolysaccharide (LPS) as a model. ROS formation was tested in cultured macrophages, in blood and in vivo. PP-H reacts with reactive oxidant species generating the stable nitroxide radical 4-phosphonooxy-TEMPO. It was shown that a 5-h treatment of macrophages with LPS (1 .mu.g/mL) leads to a threefold increase in superoxide formation as demonstrated using superoxide dismutase. Formation of reactive oxidant species 5 h after LPS (1 mg/kg) treatment of Fischer rats was analyzed in arterial blood; formation of reactive oxidant species in LPS-treated animals increased by a factor of 2.2 and was dependent upon the LPS dose. Diphenyleneiodonium (0.1 mM) inhibited formation of LPS-stimulated reactive oxidant species by 80%. We suggest that this test could be used as a noninvasive diagnostic tool for inflammation-induced oxidative stress.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L113 ANSWER 4 OF 42 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:185734 CAPLUS
DOCUMENT NUMBER: 132:317988
TITLE: N-t-Butyl **hydroxylamine**, a hydrolysis product of .alpha.-phenyl-N-t-butyl nitrone, is more potent in delaying senescence in human lung fibroblasts
AUTHOR(S): Atamna, Hani; Paler-Martinez, Andres; Ames, Bruce N.
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, Department of Molecular and Cell Biology, University of California, Berkeley, CA, 94720-3202, USA
SOURCE: Journal of Biological Chemistry (2000), 275(10), 6741-6748
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .alpha.-Phenyl-N-t-Bu nitrone (PBN), a spin trap, scavenges hydroxyl radicals, protects tissues from oxidative injury, and delays senescence of both normal human lung fibroblasts (IMR90) and senescence-accelerated mice. N-t-Bu hydroxylamine and benzaldehyde are the breakdown products of PBN. N-t-Bu hydroxylamine delays senescence of IMR90 cells at concns. as low as 10 .mu.M compared with 200 .mu.M PBN to produce a similar effect, suggesting that N-t-Bu hydroxylamine is the active form of PBN. N-Benzyl hydroxylamine and N-Me hydroxylamine compds. unrelated to PBN were also effective in delaying senescence, suggesting the active functional group is the N-hydroxylamine. All the N-hydroxylamines tested significantly decreased the endogenous prodn. of oxidants, as measured by the oxidn. of 2',7'-dichlorodihydrofluorescin and the increase in the GSH/GSSG ratio. The acceleration of senescence induced by hydrogen peroxide is reversed by the N-hydroxylamines. DNA damage, as detd. by the level of apurinic/apyrimidinic sites, also decreased significantly following treatment with N-hydroxylamines. The N-hydroxylamines appear to be effective through mitochondria; they delay age-dependent changes in mitochondria as measured by accumulation of rhodamine-123, they prevent redn. of cytochrome CFeIII by superoxide radical, and they reverse an age-dependent decay of mitochondrial aconitase, suggesting they react with the superoxide radical.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L113 ANSWER 5 OF 42 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:250903 CAPLUS
DOCUMENT NUMBER: 133:116965
TITLE: Sensitive ESR determination of intracellular **oxidative stress** by using acyl-protected **hydroxylamines** as new spin reagents
AUTHOR(S): Itoh, Osamu; Aoyama, Masaaki; Yokoyama, Hidekatsu; Obara, Heitaro; Ohya, Hiroaki; Kamada, Hitoshi
CORPORATE SOURCE: Institute of Life Support Technology, Yamagata Techniopolis Foundation, Yamagata, 990-2473, Japan
SOURCE: Chemistry Letters (2000), (4), 304-305
CODEN: CMLTAG; ISSN: 0366-7022
PUBLISHER: Chemical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several acyl-protected hydroxylamines were synthesized as new spin reagents for ESR measurements of intracellular oxidative stress. These compds. were stable non-radical compds., but were easily deprotected with esterase to yield hydroxylamines, which were oxidized by oxidants to yield ESR- detectable nitroxide radical. Using an acyl-protected hydroxylamine, a highly sensitive ESR detn. procedure was successfully conducted to

analyze oxidative stress in human leukocytes.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L113 ANSWER 6 OF 42 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:436213 CAPLUS
DOCUMENT NUMBER: 127:55919
TITLE: **Hydroxylamine** derivatives useful for enhancing molecular chaperon production and the preparation thereof
INVENTOR(S): Vigh, Laszlo; Literati Nagy, Peter; Szilbereky, Jeno; Uerogdi, Laszlo; Jednakovits, Andrea; Jaszlits, Laszlo; Biro, Katalin; Marvanyos, Ede; Barabas, Mihaly; Hegedues, Erzsebet; Koranyi, Laszlo; Kuerthy, Maria; Balogh, Gabor; Horvath, Ibolya; Torok, Zsolt; Udvardy, Eva; Dorman, Gyorgy; Medzihradszky, Denes; Mezes, Bea; Kovacs, Eszter; Duda, Erno; Farkas, Beatrix; Glatz, Attila; et al.
PATENT ASSIGNEE(S): Hung.
SOURCE: PCT Int. Appl., 179 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9716439	A1	19970509	WO 1996-HU64	19961101
W: AU, BG, BR, CA, CN, CZ, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
HU 76659	A2	19971028	HU 1995-3141	19951102
CA 2209167	AA	19970509	CA 1996-2209167	19961101
AU 9673263	A1	19970522	AU 1996-73263	19961101
AU 720195	B2	20000525		
EP 801649	A2	19971022	EP 1996-935195	19961101
EP 801649	B1	20020807		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1177351	A	19980325	CN 1996-192305	19961101
BR 9607565	A	19990720	BR 1996-7565	19961101
AT 221880	E	20020815	AT 1996-935195	19961101
ES 2176502	T3	20021201	ES 1996-935195	19961101
NO 9703059	A	19970902	NO 1997-3059	19970701

PRIORITY APPLN. INFO.:

HU 1995-3141	A	19951102
HU 1996-3919	A	19960209
HU 1996-29820	A	19961004
WO 1996-HU64	W	19961101
WO 1996-HU664		19961101

OTHER SOURCE(S): MARPAT 127:55919
AB A method of increasing expression of a mol. chaperon by a cell and/or enhancing the activity of a mol. chaperon in cells is provided. The method comprises treating a cell that is exposed to a physiol. stress which induces expression of a mol. chaperon by the cell with an effective amt. of a certain hydroxylamine deriv. to increase the stress. Alternatively, a hydroxylamine deriv. can be administrated to a cell before it is exposed to a physiol. stress which induces expression of a mol. chaperon by the cell. Preferably, the cell to which a hydroxylamine deriv. is administered is a eukaryotic cell. The invention also provides novel hydroxylamine derivs. falling within the scope of the formulas AZC(X):NOR (A = alkyl, substituted alkyl, aralkyl, substituted aralkyl, heteroaryl, etc.; Z = covalent bond, O, or NR3, where R3 = H, alkyl,

substituted alkyl, aryl, etc.; R = alkyl or substituted alkyl; X = halo, substituted hydroxy or amino, substituted amino; R' = H, alkyl, substituted alkyl, aryl, substituted aryl, etc.) and AZC(:X)N(R')OR (A = alkyl, substituted alkyl, aralkyl, substituted aralkyl, heteroaryl, etc.; Z = covalent bond, O, or NR3, where R3 = H, alkyl, substituted alkyl, aryl, etc.; R = alkyl or substituted alkyl; X =O, imino, or substituted imino; R' = H, alkyl, substituted alkyl, aryl, substituted aryl, etc.) as well as pharmaceutical and/or cosmetic compns. comprising the said compds.

L113 ANSWER 7 OF 42 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:799983 CAPLUS
DOCUMENT NUMBER: 128:136483
TITLE: Both **hydroxylamine** and nitroxide protect cardiomyocytes from **oxidative stress**
AUTHOR(S): Zhang, Renliang; Pinson, Arie; Samuni, Amram
CORPORATE SOURCE: Department of Molecular Biology, Hadassah Medical School, Hebrew University, Jerusalem, 91120, Israel
SOURCE: Free Radical Biology & Medicine (1997), Volume Date 1998, 24(1), 66-75
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The unique anti-oxidative activity of nitroxide radicals protecting against reactive oxygen-derived species (ROS) has been recently demonstrated in several model systems. The present study focuses on the activity of nitroxide and of its reduced form in cultured rat ventricular cardiomyocytes exposed to O2- and H2O2 generated by hypoxanthine (HX) and xanthine oxidase (XO). To evaluate cell injury, spontaneous beating, leakage of lactate dehydrogenase (LDH), and depletion of cellular ATP were detd. The protective effect of 4-OH-2,2,6,6-tetramethyl-piperidine-N-oxyl (TPL) was compared with that of 4-OH-2,2,6,6-tetramethyl-1-hydroxypiperidine (TPL-H) and of several common anti-oxidants. A rapid exchange between TPL and TPL-H, is mediated by cellular metab. and through reactions with ROS. In particular, TPL under O2- flux is oxidized to oxo-ammonium cation (TPL+) which comproportionates with TPL-H yielding two nitroxide radicals. Because this exchange limits the distinction between the biol. activities of TPL and TPL-H, NADH which can reduce TPL+ was included in order to maintain the nitroxide in its reduced form. The results demonstrate that both TPL and TPL-H protect cardiomyocytes against beating loss and LDH leakage. Conversely, cellular ATP depletion induced by HX/XO is inhibited by TPL-H, though not by TPL, suggesting that different mechanisms underlie their protective activities. Through a flip-flop between the two forms, which coexist in the system, the levels of TPL-H and TPL are continuously replenished. The conversion, upon reaction, of each antioxidant into the other one enables them, contrary to common antioxidants which operate in a stoichiometric mode, to act catalytically.

L113 ANSWER 8 OF 42 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:220557 CAPLUS
DOCUMENT NUMBER: 126:207531
TITLE: 2,4-Disulfonylphenyl-tert-butyl nitrone and its salts as pharmaceutical free radical-trapping agents
INVENTOR(S): Carney, John M.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; University of Kentucky Research Foundation
SOURCE: S. African, 48 pp.
CODEN: SFXXAB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ZA 9504297	A	19960124	ZA 1995-4297	19950525

PRIORITY APPLN. INFO.: ZA 1995-4297 19950525

AB 2,4-Disulfonylphenyl tert-Bu nitrone (I) and its salts have superior efficacy and potency and low toxicity when used in treatment of acute oxidative damage, e.g in the central nervous system as the result of a stroke, or after cancer radiotherapy or chemotherapy. I is also useful in treatment of conditions characterized by protracted low-grade oxidative stress on the central nervous system, e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multi-infarct dementia, and retinopathy. Thus, 2-methyl-2-nitropropane was reduced with Zn/AcOH to N-(tert-butyl)hydroxylamine, which was condensed with 4-formyl-1,3-benzenedisulfonic acid to form I in 75% yield. Thus, I (50-1000 mg/kg i.p.) completely prevented neuronal loss in gerbils after brain ischemia (bilateral carotid occlusion) and reperfusion.

L113 ANSWER 9 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 4

ACCESSION NUMBER: 1998298886 EMBASE

TITLE: Studies of structure-activity relationship of nitroxide free radicals and their precursors as modifiers against oxidative damage.

AUTHOR: Krishna M.C.; DeGraff W.; Hankovszky O.H.; Sar C.P.; Kalai T.; Jeko J.; Russo A.; Mitchell J.B.; Hideg K.

CORPORATE SOURCE: K. Hideg, Inst. of Organic/Medicinal Chemistry, University of Pecs, P.O. Box 99, H-7643 Pecs, Hungary. KHIDEG@main.pote.hu

SOURCE: Journal of Medicinal Chemistry, (27 Aug 1998) 41/18 (3477-3492).
Refs: 52
ISSN: 0022-2623 CODEN: JMCMAR

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The protective effects of stable nitroxides, as well as their hydroxylamine and amine precursors, have been tested in Chinese hamster V79 cells subjected to H_2O_2 exposure at fixed concentration or exposure to ionizing radiation. Cytotoxicity was evaluated by monitoring the viability of the cells assessed by the clonogenic assay. The compounds tested at fixed concentration varied in terms of ring size, oxidation state, and ring substituents. Electrochemical studies were carried out to measure the redox midpoint potentials. The studies show that in the case of protection against H_2O_2 exposure, the protection was determined by the ring size, oxidation state, and redox midpoint potentials. In general the protection factors followed the order nitroxides > hydroxylamines > amines. Both the six- membered ring nitroxides and substituted five-membered ring nitroxides were efficient protectors. For six-membered ring nitroxides, the compounds exhibiting the lowest midpoint potentials exhibited maximal protection. In the case of X-radiation, nitroxides were the most protective though some hydroxylamines were also efficient. The amines were in some cases found to sensitize the toxicity of aerobic radiation exposure. The protection observed by the nitroxides was not dependent on the ring size. However, the ring substituents had significant influence on the protection. Compounds containing a basic side chain were found to provide enhanced protection. The results in this study suggest that these compounds are novel antioxidants which can provide cytoprotection in mammalian cells against diverse types of oxidative insult and identify structural determinants optimal for protection against individual types of damage.

L113 ANSWER 10 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002159843 EMBASE
TITLE: Reaction of carnosine with aged proteins: Another protective process?.
AUTHOR: Hipkiss A.R.; Brownson C.; Bertani M.F.; Ruiz E.; Ferro A.
CORPORATE SOURCE: A.R. Hipkiss, GKT School of Biomedical Sciences, King's College London, Guy's Campus, London Bridge, London SE1 1UL, United Kingdom. alan.hipkiss@kcl.ac.uk
SOURCE: Annals of the New York Academy of Sciences, (2002) 959/- (285-294).
Refs: 54
ISSN: 0077-8923 CODEN: ANYAA
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 020 Gerontology and Geriatrics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Cellular aging is often associated with an increase in protein carbonyl groups arising from oxidation- and glycation-related phenomena and suppressed proteasome activity. These "aged" polypeptides may either be degraded by 20S proteasomes or cross-link to form structures intractable to proteolysis and inhibitory to proteasome activity. Carnosine (.beta.-alanyl-L-histidine) is present at surprisingly high levels (up to 20 mM) in muscle and nervous tissues in many animals, especially long-lived species. Carnosine can delay senescence in cultured human fibroblasts and reverse the senescent phenotype, restoring a more juvenile appearance. As better antioxidants/free-radical scavengers than carnosine do not demonstrate these antisenescent effects, additional properties of carnosine must contribute to its antisenescent activity. Having shown that carnosine can react with protein carbonyls, thereby generating "carnosinylated" polypeptides using model systems, we propose that similar adducts are generated in senescent cells exposed to carnosine. Polypeptide-carnosine adducts have been recently detected in beef products that are relatively rich in carnosine, and carnosine's reaction with carbonyl functions generated during amino acid deamidation has also been described. Growth of cultured human fibroblasts with carnosine stimulated proteolysis of long-labeled proteins as the cells approached their "Hayflick limit," consistent with the idea that carnosine ameliorates the senescence-associated proteolytic decline. We also find that carnosine suppresses induction of heme-oxygenase-1 activity following exposure of human endothelial cells to a glycated protein. The antisenescent activity of the spin-trap agent .alpha.-phenyl-N-t-butylnitrone (PBN) towards cultured human fibroblasts resides in N-t-butyl-hydroxylamine, its hydrolysis product. As hydroxylamines are reactive towards aldehydes and ketones, the antisenescent activity of N-t-butyl-hydroxylamine and other hydroxylamines may be mediated, at least in part, by reactivity towards macromolecular carbonyls, analogous to that proposed for carnosine.

L113 ANSWER 11 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001324935 EMBASE
TITLE: On the "struggle between chemistry and biology during aging" - Implications for DNA repair apoptosis and proteolysis, and a novel route of intervention.
AUTHOR: Hipkiss A.R.
CORPORATE SOURCE: A.R. Hipkiss, Division of Biomolecular Sciences, GKT School of Biomedical Sciences, King's College London, Guy's Campus, London Bridge, London SE1 1UL, United Kingdom. alan.hipkiss@kcl.ac.uk
SOURCE: Biogerontology, (2001) 2/3 (173-178).
Refs: 51
ISSN: 1389-5729 CODEN: BIOGCN

COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 020 Gerontology and Geriatrics
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The possible effects of specific spontaneous changes in protein chemistry on age-related homeostatic dysfunction are discussed. Spontaneous racemization and isomerization of aspartic acid and deamidation of asparagine to four possible forms of aspartic acid in caspases and their substrates could profoundly alter apoptotic activity. Deamidation of asparagine residues at critically important sites of DNA glycosylases could compromise base excision repair activity. Furthermore, as oxidative damage may enhance asparagine/aspartate instability in proteins, and erroneously-synthesized proteins show increased susceptibility to oxidative attack, it is beginning to appear that the aberrant protein forms that accumulate during ageing are possibly interrelated. The role of cell growth rates in controlling constitutive proteolytic elimination of various forms of aberrant polypeptides is then discussed. Finally, it is pointed out that three recently described agents that delay senescence in cultured cells (aminoguanidine, N-t-butylhydroxylamine and kinetin) resemble carnosine in that they are also likely to react with glycoxidised proteins, as well as possess anti-oxidant activity. These observations suggest that pluripotency may be a necessary pre-requisite for effective anti-ageing activity.

L113 ANSWER 12 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000349487 EMBASE
TITLE: Use of in vitro methaemoglobin generation to study antioxidant status in the diabetic erythrocyte.
AUTHOR: Coleman M.D.
CORPORATE SOURCE: Dr. M.D. Coleman, Mechanisms of Drug Toxicity Group, Dept. of Pharmaceutical Sciences, Aston University, Aston Triangle, Birmingham B4 7ET, United Kingdom.
m.d.coleman@aston.ac.uk
SOURCE: Biochemical Pharmacology, (15 Nov 2000) 60/10 (1409-1416).
Refs: 76
ISSN: 0006-2952 CODEN: BCPCA6
PUBLISHER IDENT.: S 0006-2952(00)00333-6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Poor glycaemic control in diabetes and a combination of oxidative, metabolic, and carbonyl stresses are thought to lead to widespread non-enzymatic glycation and eventually to diabetic complications. Diabetic tissues can suffer both restriction in their supply of reducing power and excessive demand for reducing power. This contributes to compromised antioxidant status, particularly in the essential glutathione maintenance system. To study and ultimately correct deficiencies in diabetic glutathione maintenance, an experimental model would be desirable, which would provide in vitro a rapid, convenient, and dynamic reflection of the performance of diabetic GSH antioxidant capacity compared with that of non-diabetics. Xenobiotic-mediated in vitro methaemoglobin formation in erythrocytes drawn from diabetic volunteers is significantly lower than that in erythrocytes of non-diabetics. Aromatic-hydroxylamine-mediated methaemoglobin formation is GSH-dependent and is indicative of the ability of an erythrocyte to maintain GSH levels during rapid thiol consumption.

Although nitrite forms methaemoglobin through a complex GSH-independent pathway, it also reveals deficiencies in diabetic detoxification and antioxidant performance compared with non-diabetics. Together with efficient glycaemic monitoring, future therapy of diabetes may include trials of different antiglycation agents and antioxidant combinations. Equalization in vitro of diabetic methaemoglobin generation with that of age/sex-matched non-diabetic subjects might provide an early indication of diabetic antioxidant status improvement in these studies. (C) 2000 Elsevier Science Inc.

L113 ANSWER 13 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000041394 EMBASE
TITLE: Inhibition of biochemical model reactions for inflammatory processes by plant extracts: A review on recent developments.
AUTHOR: Hippeli S.; Elstner E.F.
CORPORATE SOURCE: E.F. Elstner, Lehrstuhl fur Phytopathologie, Labor fur Angewandte Biochemie, Technische Universitat Munchen, 85350 Freising-Weihenstephan, Germany. elstner@lrz.tu-muenchen.de
SOURCE: Free Radical Research, (1999) 31/SUPPL. (S81-S87).
Refs: 26
ISSN: 1071-5762 CODEN: FRARER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB All processes of oxygen activation include very reactive intermediates. Therefore, aerobic cells must cope with- and to some extent also adapt to- oxidative stress provoked for example by infections or intoxications, where these reactive intermediates accumulate. Dependent on the strength of these impact, several symptoms indicate the deviation from normal, steady-state- metabolism. Intrinsic radical scavenging processes or compounds administered with food thus have to warrant metabolic control within certain limits. Antioxidants which in many cases are free radical scavengers or quenchers of activated states comprise a wealth of classes of organic molecules including phenolics, probably as the most prominent ones. In this communication mechanisms of protection from oxidative damage are discussed. Furthermore, examples of antioxidative functions of a few important natural products in certain diseases are reported.

L113 ANSWER 14 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998401121 EMBASE
TITLE: Hydroxyguanidines inhibit peroxynitrite-induced oxidation.
AUTHOR: Southan G.J.; Salzman A.L.; Szabo C.
CORPORATE SOURCE: C. Szabo, Children's Hospital Medical Center, Division of Critical Care, 3333 Burnet Avenue, Cincinnati, OH 45229, United States
SOURCE: Free Radical Biology and Medicine, (15 Nov 1998) 25/8 (914-925).
Refs: 38
ISSN: 0891-5849 CODEN: FRBMEH
PUBLISHER IDENT.: S 0891-5849(98)00120-8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hydroxyguanidines (OHGs), including the endogenously formed N(G)-hydroxy-L-arginine (OH-arg), can react with nitric oxide (NO) and nitrogen oxides (NOx) in vitro. Therefore, we have tested OHGs and related compounds for their ability to scavenge peroxynitrite and to protect against peroxynitrite-induced oxidative processes in cells.

Hydroxyguanidine, N(G)- hydroxy-L-arginine and other N-substituted OHGs, dose-dependently inhibited the in vitro oxidation of dihydrorhodamine (DHR) by peroxynitrite (PN), with similar or better efficacy than glutathione or cysteine. Amidoximes, aminoguanidines and O-substituted OHGs were less effective, and guanidines were without effect. In contrast to their effects on DHR oxidation, OHGs exerted only minimal inhibitory effects on the hydroxylation of benzoate by PN, suggesting that OHGs do not react with the activated isomer of peroxynitrous acid. Selected compounds were tested for protection against PN- induced suppression of mitochondrial respiration and protein oxidation in cultured J774 murine macrophages. Aminoguanidines afforded some protection against the effects of PN, but substituted-phenyl OHGs were considerably more effective. Analysis of the products of the reaction of 4-methoxybenzyl-OHG with PN showed rapid formation of nitrosated derivatives, as well as 4-methoxybenzylcyanamide and a small amount of 4-methoxybenzylurea. Nitric oxide and nitrous oxide were also evolved, but indirectly, arising from the decomposition of one of the nitrosation products. The current results demonstrate that hydroxyguanidines react with PN to protect cells against PN- mediated injury and may be more effective than the endogenous antioxidants cysteine and glutathione.

L113 ANSWER 15 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998001691 EMBASE
TITLE: Both hydroxylamine and nitroxide protect cardiomyocytes from oxidative stress.
AUTHOR: Zhang R.; Pinson A.; Samuni A.
CORPORATE SOURCE: A. Samuni, Molecular Biology, Medical School, Hebrew University, Jerusalem 91120, Israel
SOURCE: Free Radical Biology and Medicine, (1998) 24/1 (66-75).
Refs: 36
ISSN: 0891-5849 CODEN: FRBMEH
PUBLISHER IDENT.: S 0891-5849(97)00165-2
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The unique anti-oxidative activity of nitroxide radicals protecting against reactive oxygen-derived species (ROS) has been recently demonstrated in several model systems. The present study focuses on the activity of nitroxide and of its reduced form in cultured rat ventricular cardiomyocytes exposed to O2.cntdot.- and H2O2 generated by hypoxanthine (HX) and xanthine oxidase (XO). To evaluate cell injury, spontaneous beating, leakage of lactate dehydrogenase (LDH), and depletion of cellular ATP were determined. The protective effect of 4-OH-2,2,6,6-tetramethyl-piperidine-N-oxyl (TPL) was compared with that of 4-OH-2,2,6,6-tetramethyl-1-hydroxypiperidine (TPL-H) and of several common anti-oxidants. A rapid exchange between TPL and TPL-H, is mediated by cellular metabolism and through reactions with ROS. In particular, TPL under O2.cntdot.- flux is oxidized to oxo-ammonium cation (TPL+) which comproportionates with TPL-H yielding two nitroxide radicals. Because this exchange limits the distinction between the biological activities of TPL and TPL-H, NADH which can reduce TPL+ was included in order to maintain the nitroxide in its reduced form. The results demonstrate that both TPL and TPL- H protect cardiomyocytes against beating loss and LDH leakage. Conversely, cellular ATP depletion induced by HX/XO is inhibited by TPL-H, though not by TPL, suggesting that different mechanisms underlie their protective activities. Through a flip-flop between the two forms, which coexist in the system, the levels of TPL-H and TPL are continuously replenished. The conversion, upon reaction, of each antioxidant into the other one enables them, contrary to common antioxidants which operate in a stoichiometric mode, to

act catalytically.

L113 ANSWER 16 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97318725 EMBASE
DOCUMENT NUMBER: 1997318725
TITLE: Bimoclomol: A nontoxic, hydroxylamine derivative with stress protein- inducing activity and cytoprotective effects.
AUTHOR: Vigh L.; Literati P.N.; Horvath I.; Torok Z.; Balogh G.; Glatz A.; Kovacs E.; Boros I.; Ferdinandy P.; Farkas B.; Jaszlits L.; Jednakovits A.; Koranyi L.; Maresca B.
CORPORATE SOURCE: L. Vigh, Institute of Biochemistry, Biological Research Center, Hungarian Academy of Sciences, Temesvari krt. 62, 6721 Szeged, Hungary
SOURCE: Nature Medicine, (1997) 3/10 (1150-1154).
Refs: 40
ISSN: 1078-8956 CODEN: NAMEFI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Preservation of the chemical architecture of a cell or of an organism under changing and perhaps stressful conditions is termed homeostasis. An integral feature of homeostasis is the rapid expression of genes whose products are specifically dedicated to protect cellular functions against stress. One of the best known mechanisms protecting cells from various stresses is the heat-shock response which results in the induction of the synthesis of heat-shock proteins (HSPs or stress proteins). A large body of information supports that stress proteins - many of them molecular chaperones - are crucial for the maintenance of cell integrity during normal growth as well as during pathophysiological conditions, and thus can be considered 'homeostatic proteins.' Recently emphasis is being placed on the potential use of these proteins in preventing and/or treating diseases. Therefore, it would be of great therapeutic benefit to discover compounds that are clinically safe yet able to induce the accumulation of HSPs in patients with chronic disorders such as diabetes mellitus, heart disease or kidney failure. Here we show that a novel cytoprotective hydroxylamine derivative, [2- hydroxy-3-(1-piperidinyl) propoxy]-3-pyridinecarboximidoil-chloride maleate, Bimoclomol, facilitates the formation of chaperone molecules in eukaryotic cells by inducing or amplifying expression of heat-shock genes. The cytoprotective effects observed under several experimental conditions, including a murine model of ischemia and wound healing in the diabetic rat, are likely mediated by the coordinate expression of all major HSPs. This nontoxic drug, which is under Phase II clinical trials, has enormous potential therapeutic applications.

L113 ANSWER 17 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95351283 EMBASE
DOCUMENT NUMBER: 1995351283
TITLE: Inhibition of succinate:ubiquinone reductase and decrease of ubiquinol in nephrotoxic cysteine S-conjugate-induced oxidative cell injury.
AUTHOR: Van de Water B.; Zoeteweij J.P.; De Bont H.J.G.M.; Nagelkerke J.F.
CORPORATE SOURCE: Sylvius Laboratory, Division of Toxicology, P.O. Box 9503,2300 RA Leiden, Netherlands
SOURCE: Molecular Pharmacology, (1995) 48/5 (928-937).

ISSN: 0026-895X CODEN: MOPMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The role of complex II in the cellular protection against oxidative stress was investigated in freshly isolated rat renal proximal tubular cells (PTC) with the use of the nephrotoxin S-(1,2-dichlorovinyl)-L-cysteine (DCVC). DCVC caused oxidative stress in PTC as determined by flow cytometry with dihydrorhodamine-123; this fluorescent probe is readily oxidized by primary hydroperoxides such as those formed during lipid peroxidation. The oxidative stress could be prevented by inhibition of the .beta.-lyase-mediated formation and covalent binding to cellular macromolecules of reactive DCVC metabolites, with amino oxyacetic acid (AOA), or by the antioxidant N,N'-diphenyl=p- phenylenediamine. Both AOA and DPPD also prevented cell death. The DCVC- induced oxidative stress was associated with a decrease in the succinate:ubiquinone reductase (SQR) activity of complex II, whereas NADH:ubiquinone reductase activity of complex I remained unaffected. AOA prevented the effect on SQR activity, whereas N,N'-diphenyl-p- phenylenediamine did not. Inhibition of SQR activity with thenoyl trifluoracetone (TTFA) potentiated the DCVC-induced oxidative cell injury, suggesting the involvement of SQR activity in an antioxidant pathway. To investigate this in greater detail, PTC were treated with an inhibitor of cytochrome-c-oxidase, KCN, in a buffer containing glycine, which prevents cell death by KCN. Glycine did not affect cell death by DCVC. KCN prevented the DCVC-induced oxidative stress and cell death. KCN cytoprotection could be prevented by inhibition of SQR activity with oxaloacetate or TTFA, whereas inhibition of either complex I or III with rotenone and antimycin, respectively, did not prevent it. The effect of DCVC on complex II was associated with a decrease in the cellular amount of reduced ubiquinone (QH2); the KCN-mediated cytoprotection was related to a 60% increase of cellular QH2. Rotenone almost completely inhibited ubiquinone reduction even in the presence of KCN, whereas oxaloacetate in combination with KCN resulted in QH2 levels comparable to control. This suggests that the SQR activity by complex II rather than the cellular content of reduced ubiquinone (QH2) is important as a part of the cellular antioxidant machinery in the cytoprotection against oxidative stress.

L113 ANSWER 18 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93123535 EMBASE
DOCUMENT NUMBER: 1993123535
TITLE: A comparative study of the toxicity of chemically reactive xenobiotics towards adherent cell cultures: Selective attenuation of menadione toxicity by buthionine sulphoximine pretreatment.
AUTHOR: Riley R.J.; Spielberg S.P.; Leeder J.S.
CORPORATE SOURCE: Fisons Research Development Labs, Biochemistry Department, Drug Metabolism Section, Bakewell Road,Loughborough, Leics LE11 0RH, United Kingdom
SOURCE: Journal of Pharmacy and Pharmacology, (1993) 45/4 (263-267).
ISSN: 0022-3573 CODEN: JPPMAB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Metabolic activation to reactive intermediates is a prerequisite for many

forms of chemically-induced toxicity. Hepa lclc-9 cells were exposed to varying concentrations of several reactive metabolites implicated in adverse drug reactions and the toxicity of the compounds assessed using applied fluorescence technology. Cytotoxicity was assessed using the fluorescence of 2', 7'-bis-(2-carboxyethyl)-5-(6)-carboxy-fluorescein as an index of cell viability. The role of glutathione in cellular defence against these chemicals was investigated by pretreating the target cells overnight with buthionine sulphoximine, a specific inhibitor of glutathione synthesis. Depletion of intracellular glutathione augmented the toxicity of N-acetyl-p-benzoquinone imine (1.5-3-fold at 100 and 10 .mu.M). Toxicity produced by the hydroxylamine of sulphamethoxazole (500 .mu.M) was dependent entirely on pretreatment of the cells with buthionine sulphoximine (% cell death = 33 .+-. 16 compared with 0 .+-. 4 in untreated cells, P<0.05). By contrast, the lethal effects of the model quinone, menadione, were attenuated markedly following glutathione depletion. The data obtained suggest that this assay, previously used with suspension cultures, may be useful in the rapid in-vitro screening of putative reactive intermediates. Moreover, the application of such methodology should prove beneficial for the elucidation of cellular mechanisms of defence and detoxification.

L113 ANSWER 19 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78255834 EMBASE
DOCUMENT NUMBER: 1978255834
TITLE: Persistent nucleoli in cultured Yoshida sarcoma cells treated in vitro with carcinogenic and non carcinogenic derivatives of 4 nitroquinoline 1 oxide.
AUTHOR: Isaka H.; Koura S.; Koura M.; et al.
CORPORATE SOURCE: I Dept. Pathol., Fac. Med., Univ. Kagoshima, Japan
SOURCE: Acta Medica Universitatis Kagoshimaensis, (1977) 19/2 (61-69).
CODEN: AMUKAC
COUNTRY: Japan
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
016 Cancer
030 Pharmacology
005 General Pathology and Pathological Anatomy
LANGUAGE: English

AB The nucleolus is the most obvious structure in interphase nuclei of animal cells. In mitotic process of the cells, it is generally accepted that nucleoli disintegrate at late prophase and are no longer detectable at metaphase. However, persistent nucleoli in metaphase or later mitotic stages are occasionally reported in cultured animal cells. Heath (1954) reported that nucleoli of chick embryo heart cells persisted from prophase to telophase, when the cells were brought into a culture medium containing cobalt chloride. On the other hand, Hsu et al. (1964) described persistent nucleoli in metaphase of Chinese hamster cells in vitro treated with fluorodeoxyuridine and thymidine. They thought at first that they had induced persistent nucleoli in the cells by treatment with these substances. Later, they concluded that persistent nucleoli were not a result of these treatment but merely a variation of nucleolar behaviors in mitosis. They reported persistent nucleoli in various kinds of metaphase cells in vitro. Love and Suskind (1961) also demonstrated the persistence of nucleoli in cancerous and non-cancerous mammalian cells in culture. Similar results were presented by Heneen and Nichols (1966) with various culture lines of cells. According to Hsu et al. (1965), persistent nucleoli in metaphase are detected as bodies attached to the chromosome, or bodies free in the cytoplasm. In metaphase cells without nucleolar bodies as such, amorphous nucleolar substances are noted to attach to the chromosome. Some of the nucleolar substances attached to certain regions of chromosomes may develop to the nucleolar organizers. The nucleolar substances and bodies attached to the chromosomes may move together with

the chromosomes during anaphase. These findings were supported by electron microscopic investigations.The present report deals with the frequency of persistent nucleoli in cultured Yoshida cells exposed to carcinogenic and non carcinogenic derivatives of 4NQO.

L113 ANSWER 20 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 78043099 EMBASE
DOCUMENT NUMBER: 1978043099
TITLE: [Tests for the determination of carcinogenic properties of mycotoxins].
TESTS UTILISABLES POUR LA DETECTION DES POTENTIALITIES CANCEROGENES DES MYCOTOXINES.
AUTHOR: Moule Y.; Chany E.; Sarasin A.
CORPORATE SOURCE: Inst. Rech. Sci. Cancer, Villejuif, France
SOURCE: Cahiers de Nutrition et de Dietetique, (1976) 11/21 sup. (49-58).
CODEN: CNDQA8
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
017 Public Health, Social Medicine and Epidemiology
016 Cancer
LANGUAGE: French

L113 ANSWER 21 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 76001584 EMBASE
DOCUMENT NUMBER: 1976001584
TITLE: Breakage of a DNA protein complex induced by 4 nitroquinoline 1 oxide, 4 nitropyridine 1 oxide, and their derivatives in cultured mouse fibroblasts.
AUTHOR: Andoh T.; Ide T.; Saito M.; Kawazoe Y.
CORPORATE SOURCE: Dept. Virol., Inst. Med. Sci., Univ. Tokyo, Japan
SOURCE: Cancer Research, (1975) 35/3 (521-527).
CODEN: CNREA8
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
016 Cancer
030 Pharmacology
LANGUAGE: English
AB The effects of a number of 4 nitroquinoline 1 oxide and 4 nitropyridine 1 oxide derivatives, with varying carcinogenic potencies, on the scission of proteins linking DNA were studied in cultured mouse fibroblasts, strain L.P3. With twenty two 4 nitroquinoline 1 oxide derivatives and twelve 4 nitropyridine 1 oxide derivatives tested, an excellent correlation was found between the scission effect of each compound and its carcinogenicity. All carcinogens, whether strong or weak, showed positive results in the scission test. Strong carcinogens such as 4 nitroquinoline 1 oxide, 2 methyl 4 nitroquinoline 1 oxide, 6 methyl 4 nitroquinoline 1 oxide, 6 chloro 4 nitroquinoline 1 oxide, and 4 hydroxyaminoquinoline 1 oxide induced the scission at a low concentration of 1 x 10-5 M, while weak carcinogens such as 3 methyl 4 nitroquinoline 1 oxide, 6 n butyl 4 nitroquinoline 1 oxide, 6 tert butyl 4 nitroquinoline 1 oxide, 6 n hexyl 4 nitroquinoline 1 oxide, and 6 carboxy 4 nitroquinoline 1 oxide only produced the same effect at dose levels higher than 5 x 10-5 M. On the other hand, some noncarcinogenic derivatives such as 8 nitroquinoline 1 oxide, 4 hydroxy quinoline 1 oxide, 4 aminoquinoline 1 oxide, and 6 nitroquinoline could not induce the scission, while other noncarcinogens such as 3 nitroquinoline 1 oxide, 5 nitroquinoline 1 oxide, and 5 nitroquinoline did induce scission at concentrations higher than 1 x 10-4 M. Throughout these tests, the effective concentrations of active compounds were generally much lower than the concentration at which the compounds were cytotoxic. The implication of the results and the feasibility of the present method of analysis as a screening procedure for

potential carcinogens and mutagens are discussed.

L113 ANSWER 22 OF 42 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1992-44725 DRUGU C P B
TITLE: Hypoxia-Selective-Antitumor Agents. 5. Synthesis of Water-Soluble Nitroaniline Mustards with Selective Cytotoxicity for Hypoxic Mammalian Cells.
AUTHOR: Palmer B D; Wilson W R; Cliffe S; Denny W A
LOCATION: Auckland, New Zealand
SOURCE: J.Med.Chem. (35, No. 17, 3214-22, 1992) 3 Fig. 3 Tab. 45 Ref.
CODEN: JMCMAR ISSN: 0022-2623
AVAIL. OF DOC.: Cancer Research Laboratory, Department of Pathology, University of Auckland School of Medicine, Private Bag, Auckland, New Zealand.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB A series of 4-nitroaniline and 2,4-dinitroaniline mustards was prepared bearing hydrophilic side chains attached via an electron-withdrawing carboxamide group, designed as water-soluble hypoxia-selective cytotoxic agents, having adequate reduction potentials to facilitate reductive metabolism of the nitro group to an electron-donating amine or **hydroxylamine**. **Compounds** were **tested** for hypoxia-selective cytotoxicity vs. CHO (AA8 and UV4) cells. The most selective agents were SN-23862 (20) and CB-1954 (23). Compound (20) was a less efficient substrate than (23) for the major aerobic nitroreductase from rat Walker tumor cells, DT-diaphorase (DTD); lack of aerobic bioactivation of (20) by DTD may explain its higher hypoxic selectivity compared with (23).

L113 ANSWER 23 OF 42 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1990-23103 DRUGU P B
TITLE: Biologically Active Metal-Independent Superoxide Dismutase Mimics.
AUTHOR: Mitchell J B; Samuni A; Krishna M C; DeGraff W G; Ahn M S; Samuni U
LOCATION: Bethesda, Maryland, United States; Jerusalem, Israel
SOURCE: Biochemistry (29, No. 11, 2802-07, 1990) 6 Fig. 2 Tab. 33 Ref.
CODEN: BICHAW ISSN: 0006-2960
AVAIL. OF DOC.: Radiation Oncology Branch, Clinical Oncology Program, Division of Cancer Treatment, N.C.I., N.I.H., Bethesda, Maryland 20892, U.S.A. (7 authors).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB Various stable nitroxides including 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), 4-hydroxy-TEMPO (TEMPOL) (both Aldrich), 2-ethyl 2,4,4-trimethyloxazolidine 3-oxyl (OXANO) and spiro(cyclohexane 1,2'-(4',4'-dimethyloxazolidine 3'-oxyl)) (CHD) showed superoxide dismutase (SOD)-like activity. These SOD mimics, like desferrioxamine (DF, CIBA-Geigy), **protected** Chinese hamster V79 **cells** from damage induced by hypoxanthine (Calbiochem-Boehr.) xanthine oxidase (Sigma-Chem.) and H2O2 (Fisher Sci.), although they exhibited no catalase-like activity. The nitroxide SOD mimics rapidly oxidized DNA-FeII and thus may interrupt the Fenton reaction and prevent formation of OH radicals and/or high oxidation states of metal ions.

L113 ANSWER 24 OF 42 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1988-17112 DRUGU B P
TITLE: Soybean Lipoxygenase-Catalyzed Oxidations by Linoleic Acid

Hydroperoxide: Different Reducing Substrates and Dehydrogenation of Phenidone and BW 755C.
AUTHOR: Mansuy D; Cucurou C; Biatry B; Battioni J P
LOCATION: Paris, France
SOURCE: Biochem.Biophys.Res.Commun. (151, No. 1, 339-46, 1988) 2 Fig. 2 Tab. 22 Ref.
CODEN: BBRCA9 ISSN: 0006-291X
AVAIL. OF DOC.: Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques (UA 400 CNRS), Universite Rene Descartes, 45 Rue des Saints-Peres, 75270 Paris, Cedex 06, France.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB Phenidone (PD) was not a substrate for dioxygenation by soybean lipoxygenase (L), but reduced L-Fe(III) to L-Fe(II). PD was dioxygenated by 13-hydroperoxy 9Z,11E octadecadienoic acid (HP), catalyzed by L, giving 4,5-dehydro-PD. In the presence of L, HP dioxygenated BW-755C (Wellcome), 1-phenyl-3-amino 2-pyrazoline (PA), pyrocatechol (PC), nordihydroguaiaretic acid (ND), 4-aminophenol (AP), 2-hydrazinopyridine (HZ), N-hydroxyamphetamine (HA), N-phenyl-benzoylhydrazide (BH), 4-methyl benzaldehyde 4'-bromophenylhydrazone (MB) and to lesser extents guaiacol (GU), vitamin E and phenylhydrazine (PZ). Naproxen, indomethacin, ketoprofen (Rhone-Poulenc), benoxaprofen, 1-phenyl-2-methyl 3-pyrazolidone, 4,5-dehydro-PD, phenol, resorcinol, aniline and acetaminophen were not dioxygenated by HP and L.

L113 ANSWER 25 OF 42 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 1988-10770 DRUGU M S
TITLE: Role of Dapsone **Hydroxylamine** in Dapsone-Induced Hemolytic Anemia.
AUTHOR: Grossman S J; Jollow D J
LOCATION: Charleston, South Carolina, United States
SOURCE: J.Pharmacol.Exp.Ther. (244, No. 1, 118-25, 1988) 8 Fig. 1 Tab. 25 Ref.
CODEN: JPETAB ISSN: 0022-3565
AVAIL. OF DOC.: Department of Pharmacology, Medical University of South Carolina, 171 Ashley Ave., Charleston , SC 29425, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB Hemolysis was quantitated following i.p. dapsone (DS) and synthesized metabolites, monoacetyl-DS (MADDS) and DS- and MADDS-**hydroxylamine** (MADDS-NOH, DDS-NOH) in rats pretreated with i.v. 51Cr-labeled rat erythrocytes (51Cr-RBC) and following i.v. administration of 51Cr-RBC exposed to **test drugs** in vitro. Data demonstrate that DS-induced hemolytic anemia is due to a direct action of its N-hydroxyl metabolites on erythrocytes, provoking a rapid, selective sequestration by the spleen. A cumulative toxic action was indicated, consistent with the concept of hemolytic **damage** by continued **'oxidative stress'**.

L113 ANSWER 26 OF 42 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.DUPLICATE
ACCESSION NUMBER: 2000:30417469 BIOTECHNO
TITLE: The effects of nitroxide radicals on **oxidative** DNA **damage**
AUTHOR: Damiani E.; Kalinska B.; Canapa A.; Canestrari S.; Wozniak M.; Olmo E.; Greci L.
CORPORATE SOURCE: Dr. E. Damiani, Dipartimento Sci. Materiali/Terra, Universita, Via Brecce Bianche, I-60131 Ancona, Italy. E-mail: liz@popcsi.unian.it
SOURCE: Free Radical Biology and Medicine, (15 APR 2000), 28/8

Searched by Barb O'Bryen, STIC 308-4291

(1257-1265), 54 reference(s)
CODEN: FRBMEH ISSN: 0891-5849
PUBLISHER ITEM IDENT.: S0891584900002422
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The indolinonic and quinolinic aromatic nitroxides synthesized by us are a novel class of biological **antioxidants**, which afford a good degree of protection against free radical-induced oxidation in different lipid and protein systems. To further our understanding of their **antioxidant** behavior, we thought it essential to have more information on their effects on DNA exposed to free radicals. Here, we report on the results obtained after exposure of plasmid DNA and calf thymus DNA to peroxyl radicals generated by the water-soluble radical initiator, 2,2'-azobis(2-amidinopropane)dihydrochloride (AAPH), and the protective effects of the aromatic nitroxides and their **hydroxylamines**, using a simple in vitro assay for DNA damage. In addition, we also tested for the potential of these nitroxides to inhibit hydroxyl radical-mediated DNA damage inflicted by Fenton-type reactions using copper and iron ions. The commercial aliphatic nitroxides 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL), and bis(2,2,6,6-tetramethyl-1-oxyl-piperidin-4-yl)sebacate (TINUVIN 770) were included for comparison. The results show that the majority of **compounds tested** protect: (i) both plasmid DNA and calf thymus DNA against AAPH-mediated **oxidative damage** in a concentration-dependent fashion (1-0.1 mM), (ii) both Fe(II) and Cu(I) induced DNA **oxidative damage**. However, all compounds failed to protect DNA against damage inflicted by the presence of the transition metals in combination with H.sub.2O.sub.2. The differences in protection between the compounds are discussed in relation to their molecular structure and chemical reactivity. Copyright (C) 2000 Elsevier Science Inc.

L113 ANSWER 27 OF 42 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
ACCESSION NUMBER: 1989:11946 BIOSIS
DOCUMENT NUMBER: BA87:11946
TITLE: PYRROXAMIDE A NONIONIC NITROXYL SPIN LABEL CONTRAST AGENT FOR MAGNETIC RESONANCE IMAGING MUTAGENESIS AND **CELL SURVIVAL**.
AUTHOR(S): GORDON D G; BRASCH R C; OGAN M D; DEEN D
CORPORATE SOURCE: CONTRAST MEDIA LAB., DEP. RADIOL., C-309, UNIV. CALIF., SAN FRANCISCO, SAN FRANCISCO, CA 94143-0628.
SOURCE: INVEST RADIOL, (1988) 23 (8), 616-620.
CODEN: INVRAV. ISSN: 0020-9996.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Pyrroxamide [N-(1-hydroxymethyl-2,3,dihydroxypropyl)-2,2,5,5-tetramethyl pyrrolidine-1-oxyl-3-carboxyamide] is a newly **tested** nonionic monomeric nitroxyl **compound** with demonstrated effectiveness for MRI contrast enhancement at doses as low as 10-3 M. Pyrroxamide and its **hydroxylamine** metabolic derivative were tested in concentrations from 10-9 to 10-2 M with a battery of cytotoxic and mutagenic assays using mammalian Chinese hamster ovary cells. Loci-specific mutation induction was examined at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and the Na+/K+ ATPase loci, both in the presence and absence of a liver microsomal metabolic activating mixture (S-9 mix). **Cell survival** and induction of sister chromatid exchanges also were studied. All tests yielded negative results indicating that pyrroxamide and **hydroxylamine** derivative were both noncytotoxic and nonmutagenic at the doses tested.

L113 ANSWER 28 OF 42 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:38655 TOXCENTER
DOCUMENT NUMBER: 97237312 PubMed ID: 9083790
TITLE: The protective role of thiols against nitric oxide-mediated cytotoxicity in murine macrophage J774 cells
AUTHOR(S): Zamora R; Matthys K E; Herman A G
CORPORATE SOURCE: Division of Pharmacology, Faculty of Medicine, University of Antwerp (UIA), Wilrijk-Antwerp, Belgium. zamora@uia.ua.ac.be
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1997 Feb 19) 321 (1) 87-96.
Journal Code: 1254354. ISSN: 0014-2999.
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 97237312
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB Nitric oxide (NO) plays an important role in the cytotoxic activity of macrophages towards tumour cells and microbial pathogens. We investigated whether alteration of intracellular thiol levels modulates the cytotoxic effects of different NO donors and lipopolysaccharide-induced NO in the murine macrophage cell lin J774A.1. The NO-releasing compound S-nitroso-N-acetylpenicillamine caused a significant concentration-dependent loss of viability of the macrophages only under glucose-limiting conditions. The cytotoxic effect of S-nitroso-N-acetylpenicillamine was prevented by the NO scavenger 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide (carboxy-PTIO). Depletion of total glutathione before exposure to S-nitroso-N-acetylpenicillamine further decrease cell viability while pretreatment with N-acetylcysteine was protective. Comparing equimolar concentrations of various NO donors including S-nitrosoglutathione, S-nitrosocysteine and 3-morpholino-sydnonimine hydrochloride, cytotoxicity appeared to be related to the relative stability of the **test compound**. Both the order of stability and the order of potency for cell killing was S-nitrosoglutathione > S-nitroso-N-acetylpenicillamine > S-nitrosocysteine = 3-morpholino-sydnonimine hydrochloride. Stimulation of the macrophages with lipopolysaccharide and interferon-gamma resulted in dose-dependent cell injury and NO production. Glutathione depletion prior to stimulation considerably decreased macrophage viability as well as the NO production. In contrast to the protective effect on S-nitroso-N-acetylpenicillamine-mediated injury, pretreatment with N-acetylcysteine did not influence the lipopolysaccharide-mediated cytotoxicity. These results demonstrate that (a) reduction in the availability of glucose and intracellular glutathione renders the cells more vulnerable to the cytotoxic effects of NO donors, (b) in this model of cytotoxicity, long-lived NO donors were more cytotoxic than short-lived NO donors, (c) the differential effects of N-acetylcysteine on S-nitroso-N-acetylpenicillamine-induced and bacterial lipopolysaccharide-mediated cytotoxicity support the existence of other toxic species different from NO or NO-related compounds with a potent cytotoxic activity in immunostimulated macrophages, and (d) other non-protein thiols like N-acetylcysteine may substitute for glutathione as a major component of the cellular **antioxidant** defense system.

L113 ANSWER 29 OF 42 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:32272 TOXCENTER
DOCUMENT NUMBER: 90216074 PubMed ID: 2323850
TITLE: In vitro and in vivo anti-tumor activity of L-glutamic acid gamma-monohydroxamate against L1210 leukemia and B16 melanoma
AUTHOR(S): Vila J; Thomasset N; Navarro C; Dore J F

CORPORATE SOURCE: INSERM U.218, Centre Leon Berard, Lyon, France
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1990 Apr 15) 45 (4) 737-43.
Journal Code: 0042124. ISSN: 0020-7136.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 90216074
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB A glutamine analogue, L-glutamic acid gamma-monohydroxamate (GAH) demonstrated complete cytotoxicity against L1210 cells in culture and marked anti-tumoral activity in vivo against L1210 leukemia and B16 melanoma. In vitro, GAH caused concentration-dependent inhibition of L1210 cell growth, with complete cell death being reached at 72 hr and at a 500 microM concentration. A minimal incubation time of 38 hr with 500 microM GAH was necessary to obtain complete cell death at 72 hr. During incubation, GAH is metabolized to **hydroxylamine**. **Hydroxylamine** acts as the active form of GAH, since the concentration-dependent inhibition of cell growth caused by **hydroxylamine** is the same as that observed with GAH. The cytotoxic effects of GAH and **hydroxylamine** on L1210 cells were not reversed or prevented by L-glutamine or L-glutamic acid and purine nucleosides but were prevented or reversed by pyruvate, 2-oxaloacetate and 2-oxoglutarate. In vivo, GAH considerably increased survival of mice bearing L1210 leukemia or a solid tumor, the B16 melanoma. Antitumor activity of GAH against L1210 leukemia and B16 melanoma was schedule-dependent. The administration of GAH 3 times daily was more effective than a twice daily treatment and the maximum ILS was observed using split-dose schedules on days 1 through 3 and 7 through 9 without noticeable toxicity. Under these conditions **hydroxylamine** is highly toxic, suggesting that in vivo GAH might act as an **hydroxylamine** releaser in the tumor cells and is not significantly metabolized in the body.

L113 ANSWER 30 OF 42 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:39509 TOXCENTER
DOCUMENT NUMBER: 89270998 PubMed ID: 2729556
TITLE: Fluorescence-based viability assay for studies of reactive drug intermediates
AUTHOR(S): Leeder J S; Dosch H M; Harper P A; Lam P; Spielberg S P
CORPORATE SOURCE: Division of Clinical Pharmacology/Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada
SOURCE: ANALYTICAL BIOCHEMISTRY, (1989 Mar) 177 (2) 364-72.
Journal Code: 0370535. ISSN: 0003-2697.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 89270998
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB Studies of drug toxicity, toxicologic structure-function relationships, **screening** of idiosyncratic **drug** reactions, and a variety of cytotoxic events and cellular functions in immunology and cell biology require the sensitive and rapid processing of often large numbers of cell samples. This report describes the development of a high-sensitivity, high-throughput viability assay based on (a) the carboxyfluorescein derivative 2'-7'-biscarboxyethyl-5(6)-carboxyfluorescein (BCECF) as a vital dye, (b) instrumentation capable of processing multiple small (less than 100 cells) samples, and (c) a 96-well unidirectional vacuum filtration plate. Double staining of cultured peripheral blood

mononuclear cells with BCECF and propidium iodide (PI) showed no overlap between PI+ (nonviable) and BCECF+ (viable) cells by flow cytometric analysis. Optimal conditions were developed for dye loading and minimizing physical cell damage and fluorescence quench during the assay procedure. The ratio of BCECF fluorescence to internal standard fluorescent particles was linear from 40 to greater than 20,000 cells with a signal:noise ratio of approximately 3 at 40 cells/well. Sulfamethoxazole **hydroxylamine** (SMX-HA) was used as a model toxic drug metabolite to explore the validity of the BCECF procedure. SMX-HA, but not its parent compound sulfamethoxazole, resulted in a dose dependent loss of cellular fluorescence and the parallel accumulation of PI+ nonviable cells. When compared to the currently used tetrazolium dye reduction viability assay, the BCECF method was 3-fold more sensitive, greater than 10-fold faster, and required 1/10-1/100 the cell numbers.

L113 ANSWER 31 OF 42 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1985:5752 TOXCENTER
DOCUMENT NUMBER: 85019081 PubMed ID: 6385585
TITLE: **Protective** activity of a **cell**-free Klebsiella vaccine in relation to different Klebsiella pneumoniae serovars
AUTHOR(S): Kurbatova E A; Egorova N B; Kiseleva B S
SOURCE: ZHURNAL MIKROBIOLOGII, EPIDEMIOLOGII I IMMUNOBIOLOGII, (1984 Aug) (8) 80-3.
Journal Code: 0415217. ISSN: 0372-9311.
COUNTRY: USSR
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 85019081
LANGUAGE: Russian
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB The capacity of dried Klebsiella cell-free vaccine, obtained from strain No. 204 by the disintegration of microbial **cells** with **hydroxylamine**, for **protecting** mice from Klebsiella septic infection caused by the homologous serovar and 9 heterologous serovars of K. pneumoniae was studied. The newly developed preparation was found capable of stimulating immunity not only to the homologous K. pneumoniae serovar, but also to other K. pneumoniae heterologous serovars: K1, K9, K11, K16, K20, K61. The protective capacity of the preparation with respect to these serovars was not inferior to that of the vaccines prepared by the same method from the corresponding homologous strains. The capacity of the vaccine to protect mice from Klebsiella sepsis was manifested irrespective of the virulence of the strains used for challenge.

L113 ANSWER 32 OF 42 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1970:48960 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA07213064401A
TITLE: Genetics of somatic mammalian cells. IX. Quantitation of mutagenesis by physical and chemical agents
AUTHOR(S): Rao, Fa-Ten; Puck, Theodore T.
CORPORATE SOURCE: Med. Center, Univ. of Colorado, Denver, CO, USA.
SOURCE: Journal of Cellular Physiology, (1969) Vol. 74, No. 3, pp. 245-57.
CODEN: JCLLAX. ISSN: 0021-9541.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1970:64401
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116

Last Updated on STN: 20021231

AB A system for inducing single gene mutations in Chinese hamster cells has been extended to produce addnl. auxotrophic mutants, and an improved method for quantitating the efficiency of single gene mutation to specific auxotrophies has been developed. Mutagenesis in the forward direction has been measured after treatment of these cells with ethyl methanesulfonate, N-methyl-N1-nitro-N-nitrosoguanidine, **hydroxylamine**, an acridine mustard (ICR-191), caffeine, and uv- and x-irradn. For each agent, the single **cell survival** curve and the efficiency of chromatid breakage and rearrangement were measured. Similar measurements were also carried out with a water-sol. carcinogen, N-nitrosomethylurea, which was effective in producing auxotrophic, somatic mutations. These results may help to illuminate the relations between cell killing, chromosomal aberration, single gene mutations, and carcinogenesis produced by various agents. The methods described can be used in routine **testing of drugs**, food additives, and environmental pollutants for mutagenic action in mammalian cells in vitro.

L113 ANSWER 33 OF 42 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:562096 TOXCENTER
DOCUMENT NUMBER: CRISP-2000-SC06387-13
TITLE: Nitroxides as Protectors Against **Oxidative Stress**
AUTHOR(S): MITCHELL J
CORPORATE SOURCE: NCI SC, NIH
SUPPORTING ORGANIZATION (SPONSORING AGENCY): U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INSTITUTES OF HEALTH, DIVISION OF CLINICAL SCIENCES - NCI
SOURCE: Crisp Data Base National Institutes of Health.
DOCUMENT TYPE: (Research)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY DATE: Entered STN: 20021200
Last Updated on STN: 20021200

AB Nitroxides (such as tempol) which have been used as EPR spin labels have been sh own to exhibit superoxide dismutase (SOD) activity and are quite effective agent s in **protecting cells** against a wide variety of **oxidative stresses** including hyd rogen peroxide, superoxide, organic hydroperoxides, redox-cycling chemotherapy d rugs, and ionizing radiation. We have demonstrated that Tempol protects both cel ls in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting h umans against radiation. Importantly, we have shown that tempol does not protect rodent tumor tissue; the mechanism of which we believe involves differential me tabolic reduction properties of normal versus tumor tissue. In vivo electron par amagnetic resonance imaging studies in a tumor-bearing animal model has shown mo re rapid reduction of nitroxides in tumor compared to normal tissue. Recent stud ies have shown that cells deficient in glucose 6 phosphate dehydrogenase (G6PD) reduce the nitroxide to the **hydroxylamine** much slower than control cells suggest ing a role for this important biochemical pathway in nitroxide reduction. We ar e presently studying G6PD status in tumor versus normal tissue. Using nitroxide spin probes, the functional EPR imaging system will also enable us to map out ox ygen levels in tissue as well as study various redox parameters of tissue.We con tinue to study the mechanism(s) of nitroxide-mediated radioprotection. Recent s tudies have shown that only the oxidized form of the nitroxide (as opposed to th e reduced form) provides radioprotection. Interestingly, when amino groups are substituted at various positions on the nitroxide ring, radioprotection increase s, suggesting the importance perhaps of binding to intracellular targets such as DNA as a necessary component of radioprotection. Studies continue toward evalua ting the radioprotective properties of tempol and other nitroxides applied topic ally to the rectum

of rats. Since the rectum is a major normal tissue damaged d uring radiotherapy for patients with prostate and/or cervix cancer, we will cons ider using tempol clinically to protect the rectum should our pre-clinical studi es prove positive. Our present studies are directed on nitroxide delivery metho ds to rectal tissue to optimize nitroxide concentration. We are also investigat ing in in vivo models, the activity of nitroxides alone or appended to macromole cules such as albumin. Since these agents readily penetrate cell membranes, they may be of use in other areas of medical research such as ischemia/reperfusion i njury studies, prevention of cataracts, inflammatory processes and aging. We ha ve recently shown that tempol administration after induced ischemia of rat brain markedly reduced the infarct volume associated with ischemia/reperfusion. Prel iminary studies have indicated that long term administration of tempol (in the f ood or drinking water) to p53 knockout mice extends their life span. p53 knocko ut mice die several months after birth due to rapid tumor induction. Tempol adm inistration extended the life span of these animals 35-70%. The mechanism of t his effect is unknown and is presently a major focus. Likewise, we have shown t hat long-term administration of tempol to mice results in weight reduction, whic h we believe impacts leptin and perhaps uncoupling proteins levels. Since nitro xides readily penetrate cell membranes and are potent **antioxidants**, they may be of use in other areas of medical research such as ischemia/reperfusion injury st udies, prevention of cataracts, inflammatory processes, and aging. Lastly, to be tter understand the effects of tempol treatment at the molecular level we have i nitiated gene expression studies using cDNA microarrays.

L113 ANSWER 34 OF 42 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:556540 TOXCENTER
DOCUMENT NUMBER: CRISP-1999-SC06387-12
TITLE: NITROXIDES AS PROTECTORS AGAINST **OXIDATIVE STRESS**
AUTHOR(S): MITCHELL J
CORPORATE SOURCE: NCI SC, NIH
SUPPORTING ORGANIZATION (SPONSORING AGENCY): U.S. DEPT. OF HEALTH AND HUMAN SERVICES; PUBLIC HEALTH SERVICE; NATIONAL INSTITUTES OF HEALTH, DIVISION OF CLINICAL SCIENCES - NCI
SOURCE: Crisp Data Base National Institutes of Health.
DOCUMENT TYPE: (Research)
FILE SEGMENT: CRISP
LANGUAGE: English
ENTRY DATE: Entered STN: 20021200
Last Updated on STN: 20021200

AB Nitroxides (such as tempol) which have been used as EPR spin labels have been sh own to exhibit superoxide dismutase (SOD) activity and are quite effective agent s in **protecting cells** against a wide variety of **oxidative stresses** including hyd rogen peroxide, superoxide, organic hydroperoxides, redox-cycling chemotherapy d rugs, and ionizing radiation. We have demonstrated that Tempol protects both cel ls in vitro and mice against ionizing radiation. Thus, the nitroxides represent a new class of radiation protectors that may have widespread use in protecting h umans against radiation. Importantly, we have shown that tempol does not protect rodent tumor tissue; the mechanism of which we believe involves differential me tabolic reduction properties of normal versus tumor tissue. In vivo electron par amagnetic resonance imaging studies in a tumor-bearing animal model has shown mo re rapid reduction of nitroxides in tumor compared to normal tissue. We have com pleted an in vitro study to identify the most efficient nitroxide for protection purposes. Over 110 nitroxides were evaluated in a structure activity relationsh ip study. We have identified 6 nitroxides that afford significantly more radiopr otection than tempol (the first nitroxide shown to have radioprotective properti es) and have also identified 3 analogs that radiosensitize aerobic cells. These agents will be evaluated and

compared with tempol in vivo. Large quantities of s everal of the six protective nitroxides are being synthesized for further study of these newly discovered protectors. We have recently shown that heme proteins exposed to oxidants form highly toxic ferryl moieties and that nitroxides detoxi fy these toxic species and confer enhanced catalase-like activity to heme specie s. Reasoning in an analogous fashion we are investigating the affects of nitroxi des as modulators of nitric oxide synthase because intermediates within the enzy me which depend on heme redox chemistry may be altered in the presence of nitrox ides. We are also investigating in in vivo models, the activity of nitroxides ap pended to macromolecules such as albumin. Since these agents readily penetrate c ell membranes, they may be of use in other areas of medical research such as isc hemia/reperfusion injury studies, prevention of cataracts, inflammatory processe s and aging. Nitroxides (such as tempol) which have been used as electron parama gnetic resonance (EPR) spin labels have been shown to exhibit superoxide dismuta se (SOD) activity and are quite effective agents in **protecting cells** against a w ide variety of **oxidative stresses** including hydrogen peroxide, superoxide, organ ic hydroperoxides, redox-cycling chemotherapy drugs, and ionizing radiation. We have demonstrated that tempol **protects** both **cells** in vitro and mice against ioni zing radiation. Different nitroxides analogues that do not influence blood press ure when administered to animals have been positively identified as radioprotect ors thus eliminating the hemodynamic concerns of tempol administration. Recent s tudies have shown that tempol does not protect rodent tumor tissue; the mechanis m of which we believe involves differential metabolic reduction properties of no rmal versus tumor tissue. In vivo EPR imaging studies in one tumor-bearing anima l model has shown more rapid reduction of nitroxides in tumor compared to normal tissue. We are presently seeking to identify and define cellular and physiologi cal factors responsible for this differential effect using our newly constructed functional EPR imaging instrumentation for small animals. Recent studies have s hown that cells deficient in glucose 6 phosphate dehydrogenase (G6PD) reduce the nitroxide to the **hydroxylamine** much slower than control cells suggesting a role for this important biochemical pathway in nitroxide reduction. We are presently studying G6PD status in tumor versus normal tissue. Using nitroxide spin probes , the functional EPR imaging system will also enable us to map out oxygen levels in tissue as well as study various redox parameters of tissue.Studies are prese ntly underway evaluating the radioprotective properties of tempol applied topica lly to the rectum of rats. Since the rectum is a major normal tissue damaged dur ing radiotherapy for patients with prostate and/or cervix cancer, we will consid er using tempol clinically to protect the rectum should our pre-clinical studies prove positive. Our present studies are directed on nitroxide delivery methods to rectal tissue to optimize nitroxide concentration.Preliminary studies have in dicated that long term administration of tempol (in the food or drinking water) to p53 knockout mice extends their life span. p53 knockout mice die several mont hs after birth due to rapid tumor induction. Tempol administration extended the life span of these animals 35-70%. The mechanism of this effect is unknown and is presently a major focus. Lastly, since these agents readily penetrate cell me mbranes and are potent **antioxidants**, they may be of use in other areas of medica l research such as ischemia/reperfusion injury studies, prevention of cataracts, inflammatory processes, and aging. It has recently been shown that tempol admin istration after induced ischemia of rat brain markedly reduced the infarct volum e associated with ischemia/reperfusion.

L113 ANSWER 35 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-103404 [09] WPIDS
CROSS REFERENCE: 2003-120430 [11]
DOC. NO. CPI: C2003-026101
TITLE: Composition useful for incorporating unnatural amino acid

in a polypeptide in vivo, has orthogonal tRNA which recognizes selector codon and orthogonal tRNA synthetase which aminoacylates tRNA with unnatural amino acid.

DERWENT CLASS: B04 C06 D16
INVENTOR(S): ANDERSON, J C; CHIN, J W; LIU, D R; MAGLIERY, T J; MEGGERS, E L; MEHL, R A; PASTRNAK, M; SANTORO, S W; SCHULTZ, P; WANG, L; ZHANG, Z
PATENT ASSIGNEE(S): (SCRI) SCRIPPS RES INST
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002086075	A2	20021031	(200309)*	EN	170

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002086075	A2	WO 2002-US12635	20020419

PRIORITY APPLN. INFO: US 2002-355514P 20020206; US 2001-285030P 20010419

AB WO 200286075 A UPAB: 20030214
NOVELTY - A composition (I) comprises an orthogonal tRNA (O-tRNA), where the O-tRNA recognizes a selector codon and the O-tRNA is preferentially aminoacylated with a unnatural amino acid by an orthogonal aminoacyl-tRNA synthetase.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising an orthogonal aminoacyl-tRNA synthetase (O-RS), which preferentially aminoacylates O-tRNA with an unnatural amino acid;

(2) a polypeptide comprising an amino acid sequence encoded by a coding polynucleotide sequence chosen from:

(a) one of the 31 base pair sequences (N1) given in the specification;

(b) a coding polynucleotide sequence that encodes a polypeptide comprising a sequence chosen from one of the 32 polypeptide sequences (P1) given in the specification;

(c) a polynucleotide which hybridizes under highly stringent conditions over substantially an entire length of a polynucleotide sequence; or

(d) a complement of the sequence of (a)-(c);

(3) a polypeptide comprising an amino acid sequence chosen from P1;

(4) a nucleic acid (III) comprising a polynucleotide sequence chosen from:

(a) the Methanococcus jannaschii mtRNA, HLAD03 (87 base pair sequence (S1) defined in the specification);

(b) optimized amber suppressor tRNA, HL325A (88 base pair sequence (S2) defined in the specification);

(c) an optimized AGGA frameshift suppressor tRNA (89 base pair sequence (S3) defined in the specification); or

(d) a polynucleotide sequence which hybridizes under highly stringent conditions over the entire length of (III);

(5) producing (IV) at least one recombinant O-RS, by generating a

library of RSs derived from at least one aminoacyl-tRNA synthetase (RS) from a first organism, selecting or screening the library of RSs for members that aminoacylate an orthogonal tRNA (O-tRNA) in the presence of an unnatural amino acid and a natural amino acid, thus providing a pool of active RSs, and selecting or screening the pool for active RSs that preferentially aminoacylate the O-tRNA in the absence of the unnatural amino acid, thus providing at least one recombinant O-RS, where at least one recombinant O-RS preferentially aminoacylates the O-tRNA with the unnatural amino acid;

(6) producing (V) a recombinant O-tRNA, by generating a library of tRNAs derived from at least one tRNA from a first organism; selecting or screening the library for tRNAs that are aminoacylated by an aminoacyl-tRNA synthetase (RS) from a second organism in the absence of a RS from the first organism, thus providing a pool of tRNAs; and selecting or screening the pool of tRNAs for members that are aminoacylated by an introduced orthogonal RS (O-RS), thus providing at least one recombinant O-tRNA, where at least one recombinant O-tRNA recognizes at least one selector codon and is not efficiency recognized by the RS from the second organism and is preferentially aminoacylated by the O-RS;

(7) producing at least one specific O-tRNA/O-RS pair, by performing (IV) and (V); and

(8) identifying (VI) an orthogonal tRNA-tRNA synthetase pair for use in an in vivo translation system of a second organism, by introducing a marker gene, a tRNA and an aminoacyl-tRNA synthetase (RS) isolated or derived from a first organism into a first set of cells from the second organism, introducing the marker gene and tRNA into a duplicate cell set from the second organism, and selecting or screening for surviving cells or for cells showing a specific screening response in the first set that fail to survive or show the response in the duplicate cell set, where the first set and duplicate cell set are grown in the presence of a selection or screening agent, where the surviving or selecting cells comprise the tRNA-tRNA synthetase pair.

USE - The orthogonal tRNA-aminoacyl-tRNA-synthetase pairs are useful to incorporate unnatural amino acid in a polypeptide in vivo.

DESCRIPTION OF DRAWING(S) - The figure shows the site-specific incorporation of unnatural amino acids into proteins in vivo.

Dwg.1/31

L113 ANSWER 36 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-103365 [09] WPIDS
DOC. NO. CPI: C2003-026068
TITLE: New covalent-binding antibody-like trapping compound selective for specific binding to target molecular structure useful in e.g. diagnostics comprises chemically modified reactive compound.
DERWENT CLASS: A89 B04 B05
INVENTOR(S): GREEN, B S
PATENT ASSIGNEE(S): (SEMO-N) SEMOREX INC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002083708	A2	20021024	(200309)*	EN	67

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002083708 A2		WO 2002-IL307	20020416

PRIORITY APPLN. INFO: US 2001-283645P 20010416

AB WO 200283708 A UPAB: 20030206

NOVELTY - A covalent-binding antibody-like trapping compound (A) selective for specific binding to a target molecular structure (B) is new. (B) comprises a chemically modified reactive compound that is selective for the target.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a combinatorial library of compounds, each containing a chemically reactive group, screened for selectivity and chemical reaction with (B) for creating (A); and

(2) preparation of (A).

ACTIVITY - None given in the source material.

MECHANISM OF ACTION - None given in the source material.

USE - Used in diagnostics, combinatorial screening genomic which includes combinatorial **screening** for **drug** discovery, proteomic and glycomic applications, environmental detection, environmental removal or chemical weapons or environmental hazards and protection from chemical weapons or environmental hazards; as a therapeutic compound and for drugs or extracorporeal treatment.

In a test, samples containing 10 mg of MIP 92-42 (control) or MIP 92-42III (test) were mixed with isopropyl alcohol (1 ml) and preincubated at room temperature for 44 hours. DPFP was then added to the samples to a final concentration of 5 mu M. The mixture was shaken and incubated for 24 hours. After 24 hours, the test and control were centrifuged for 1 minute to sediment the polymers. The percentage inhibition of butyryl choline esterase was measured and found to be for control 57% at 4.5 mu M of DPFP concentration and for test 23% at 1.5 mu M for DPFP concentration.

ADVANTAGE - (A) Are selective for the target substance (e.g. a small molecule, a macromolecule such as a protein, carbohydrate, nucleic acid, a cell or a viral particle) and have an improved apparent affinity constant at least double that of the chemically unmodified parent compound.

Dwg.0/14

L113 ANSWER 37 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-682774 [73] WPIDS
DOC. NO. NON-CPI: N2002-539050
DOC. NO. CPI: C2002-192635
TITLE: Reagent for mass spectrometric analysis of proteins for determining phosphorylation state of proteins, for **screening therapeutics** that alter phosphorylation state of protein and as diagnostic for detecting diseases.
DERWENT CLASS: B04 D16 S03 V05
INVENTOR(S): CONRADS, T P; GOSHE, M B; PANISKO, E A; VEENSTRA, T D
PATENT ASSIGNEE(S): (CONR-I) CONRADS T P; (GOSH-I) GOSHE M B; (PANI-I) PANISKO E A; (VEEN-I) VEENSTRA T D; (BATT) BATTELLE MEMORIAL INST
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002066988 A2		20020829	(200273)*	EN	46

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK

DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2002119505 A1 20020829 (200273)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002066988 A2		WO 2002-US4564	20020215
US 2002119505 A1		US 2001-788286	20010216

PRIORITY APPLN. INFO: US 2001-788286 20010216

AB WO 200266988 A UPAB: 20021113

NOVELTY - A reagent (I) for mass spectrometric analysis of proteins that satisfies the general formula (F1) or (F2).

DETAILED DESCRIPTION - A reagent (I) for mass spectrometric analysis of proteins that satisfies the general formula (F1) or (F2).

(I) satisfies the general formula B-L-PhRG (F1), where B is a binding agent that selectively binds to a capture reagent (CR), L is a linker group that comprises at least one isotopically heavy atom and a phosphorylation reactive group (PhRG) that selectively labels proteins at one or more residues that were formerly occupied by phosphate group, or satisfies the general formula B-B1-X1-(CH2)n-(X2-(CH2)m)x-X3-(CH2)p-X4-B2-PhRG (F2), where B is a binding agent, PhRG is a phosphate reactive group, B1-X1-(CH2)n-(X2-(CH2)m)x-X3-(CH2)p-X4-B2 is a linker group, where X1, X2, X3 and X4, are independently chosen from O, S, NH, NR, NRR1+, CO, COO, COS, S-S, SO, SO2, CO-NR, CS-NR1, Si-O, aryl, or diaryl, where at least one of the X1, X2, X3 and X4 groups comprises an isotopically heavy atom.

USE - (I) is useful for comparing the phosphorylation states of one or more proteins in two or more samples, involves providing a substantially chemically identical and differentially isotopically labeled protein reactive reagent (I) for each sample, reacting each sample with (I) to provide protein bound to (I), where such bound proteins are differentially labeled with stable isotopes, capturing bound proteins of the samples using the capture reagent that selectively binds the binding agent, releasing captured bound proteins from the capture reagent by disrupting the interaction between the binding agent and the capture reagent, and detecting the released bound proteins.The bound proteins in the samples are enzymatically or chemically processed to convert them into bound peptides. The protein portion of one or more of the bound proteins are sequenced by tandem mass spectrometry to identify the bound protein.

The amount of one or more phosphorylated proteins in the sample is determined by mass spectrometry and further involves introducing into a sample a known amount of one or more internal standards for each protein to be quantified. The phosphorylated amino acid residues are threonine, serine and tyrosine. The released bound proteins are separated by chromatography prior to detecting the bound proteins by mass spectrometry. Number of proteins in a single sample are detected and identified or all of the proteins in a sample are identified. The relative amounts of one or more proteins in two or more samples are determined and further involves combining differentially labeled samples, capturing bound proteins from the combined samples and measuring relative abundances of the bound proteins differentially labeled proteins. The proteins quantified are membrane proteins. The different samples contain proteins originating from different organelles or different subcellular fractions or represents proteins expressed in response to different environmental or nutritional conditions, different chemical or physical stimuli or at different times, or proteins expressed in different disease states. (I) is useful for **screening** a **therapeutic** that alters a phosphorylation state of a protein, involves contacting at least one test sample containing the protein with the therapeutic, providing at least one

control sample containing the protein, removing one or more phosphate groups from one or more amino acid residues of the protein in the test sample and control sample, tagging the test sample and the control sample with (I), and detecting the level of phosphorylation of tagged proteins in the test sample and the control sample, and determining whether the therapeutic altered the level of phosphorylation of the tagged proteins in the test sample.

(I) is useful for detecting more than one type of phosphorylated amino acid residue in a protein, involves removing the phosphate group from at least one serine residue or at least one threonine residue, removing the phosphate group from at least one tyrosine residue, tagging the serine residue or tyrosine residue with (I), tagging the tyrosine residue with (I) and detecting the tagged protein. Removing the phosphate group from serine residue or threonine residue is after the removal of phosphate group from tyrosine. Tagging serine residue or threonine residue is done after tagging the tyrosine residue (all claimed). (I) is useful for characterization of phosphorylation state of multiple proteins i.e., useful to profile the phosphorylation state of multiple proteins from tissue samples such as tumor samples, body fluids such as urine, saliva or blood, or cell cultures, as diagnostic for the detection of diseases associated with hyper- or hypo-phosphorylation of protein, for **screening** to identify **compounds** that affect the phosphorylation state of protein i.e., to identify potential therapeutic agent to alter the phosphorylation state of proteins suspected of contributing to disease, and for measuring absolute quantitative amount of proteins in sample. (I) is useful for diagnosing various diseases and for understanding protein-protein interaction and for identifying and/or detecting number of proteins in a single sample. (I) is useful as a diagnostic tool to identify subjects suffering from diseases caused by protein phosphorylation abnormalities.

ADVANTAGE - (I) is applied to peptides that are generated via enzymatic or chemical processing or is applied to proteins followed by protein sequencing. By using (I), the phosphorylation state of a specific protein is compared with a control sample without the need for protein sequencing, quantification or the use of antibodies selective for the phosphorylated protein itself.

Dwg.0/6

L113 ANSWER 38 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-457296 [49] WPIDS
DOC. NO. NON-CPI: N2001-338917
DOC. NO. CPI: C2001-138281
TITLE: New product comprising nucleic acid linked to a support, useful as DNA chip, e.g. for diagnosis and as transfection vehicle, has nucleic acid stably and covalently attached.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): GRAS, M H; LEMOINE, Y; MELNYK, O; GOUYETTE, C; GRAS-MASSE, H; HOT, D; HUOT, L; HUYNH-DINH, T; OLIVIER, C; OLLIVIER, N; WOLOWCZUK, I
PATENT ASSIGNEE(S): (CNRS) CENT NAT RECH SCI; (INSP) INST PASTEUR; (INSP) INST PASTEUR LILLE; (INSP) INST PASTEUR FONDATION; (CNRS) CNRS CENT NAT RECH SCI
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001042495 A2		20010614	(200149)*	FR	58

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC

LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
FR 2801904 A1 20010608 (200149)
AU 2001025241 A 20010618 (200161)
EP 1235839 A2 20020904 (200266) FR
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
JP 2003516159 W 20030513 (200334) 89

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001042495	A2	WO 2000-FR3427	20001207
FR 2801904	A1	FR 1999-15392	19991207
AU 2001025241	A	AU 2001-25241	20001207
EP 1235839	A2	EP 2000-988891	20001207
		WO 2000-FR3427	20001207
JP 2003516159	W	WO 2000-FR3427	20001207
		JP 2001-544367	20001207

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001025241	A	Based on	WO 200142495
EP 1235839	A2	Based on	WO 200142495
JP 2003516159	W	Based on	WO 200142495

PRIORITY APPLN. INFO: FR 1999-15392 19991207
AB WO 200142495 A UPAB: 20010831
NOVELTY - Nucleic acid product (A) attached to a support through a linker, is new.
DETAILED DESCRIPTION - Nucleic acid product (A) attached to a support through a linker. (A) is of formula SP(Ai(Yi-Z-CO-M)n)m (I)
Z' = the (i) or -X-N=CH-;
asterisk = attachment point;
X = CH2O, CH2NH or NH;
i = 0 or 1;
n = 1-16, and is 1 when i = 0;
m = 1 or more;
SP = support;
A = spacer;
Y = group linking A and Z'; and
M = nucleic acid linked to CO at the 3' or 5' end.
INDEPENDENT CLAIMS are also included for the following:
(a) method (M1) for preparing (I);
(b) method (M2) for covalent bonding of M to SP to form (I);
(c) oligonucleotides (ON), or DNA, modified at the 5'-end by attachment of tartaric acid, serine, threonine, their derivatives, or an alpha -oxoaldehyde (aOA) group;
(d) method (M3) for producing the ON or DNA;
(e) functionalized support of formula SP(Ai(Yi-B'-NH2)n)m (II);
(f) method (M4) for preparing (II);
(g) quality control method for (II);
(h) method (M5) for quantifying the functionality of (II);
(i) kit for preparing a DNA chip, i.e. (I) where SP is a solid, i and n =1 and M is DNA;
(j) method (M6) for selecting molecules by reaction with the DNA chip; and
(k) molecules selected by (M6).
B' = CH2O, CH2NH, NH or CH(CH2SH).
USE - (A) are particularly useful as DNA chips for combinatorial

chemistry, i.e. for high throughput **screening** to identify new genes or **pharmaceuticals** and for studying toxicity, also for diagnosis. Alternatively, they are useful as transfection vehicles.

ADVANTAGE - (A) are produced simply, reproducibly and inexpensively, have nucleic acids attached covalently (very stable linkage under conditions of hybridization and washing, with minimal desorption over many hybridization cycles); uses a stable, easily produced modification of nucleic acid and a stable, non-hydrolyzable functionalized support; the group used for bonding nucleic acid to the support is very reactive (compensating for low reactant concentration), and no denaturation of nucleic acid occurs (retention of optimal hybridization properties). Dwg.0/18

L113 ANSWER 39 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-527578 [44] WPIDS
DOC. NO. CPI: C1999-155047
TITLE: Transition-metal-catalyzed arylation or vinylation of hydrazines and hydrazones; giving product suitable for cyclization to give heterocycles for use as pharmaceuticals or agrochemicals.
DERWENT CLASS: B05 C02 C03
INVENTOR(S): BUCHWALD, S L; GEIS, O; WAGAW, S; GEIS, O F
PATENT ASSIGNEE(S): (MASI) MASSACHUSETTS INST TECHNOLOGY; (BUCH-I) BUCHWALD S L; (GEIS-I) GEIS O F; (WAGA-I) WAGAW S
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9943643	A2	19990902	(199944)*	EN	97
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP					
EP 1058678	A2	20001213	(200066)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
US 6235936	B1	20010522	(200130)		
US 2001031894	A1	20011018	(200166)		
JP 2002504535	W	20020212	(200215)		102
US 6465693	B2	20021015	(200271)		
EP 1058678	B1	20021211	(200282)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
DE 69904448	E	20030123	(200315)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9943643	A2		WO 1999-US4217	19990226
EP 1058678	A2		EP 1999-908515	19990226
			WO 1999-US4217	19990226
US 6235936	B1		US 1998-30936	19980226
US 2001031894	A1	Div ex	US 1998-30936	19980226
			US 2001-765072	20010118
JP 2002504535	W		WO 1999-US4217	19990226
			JP 2000-533402	19990226
US 6465693	B2	Div ex	US 1998-30936	19980226
			US 2001-765072	20010118
EP 1058678	B1		EP 1999-908515	19990226
			WO 1999-US4217	19990226
DE 69904448	E		DE 1999-604448	19990226
			EP 1999-908515	19990226
			WO 1999-US4217	19990226

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1058678	A2	Based on	WO 9943643
US 2001031894	A1	Div ex	US 6235936
JP 2002504535	W	Based on	WO 9943643
US 6465693	B2	Div ex	US 6235936
EP 1058678	B1	Based on	WO 9943643
DE 69904448	E	Based on	EP 1058678
		Based on	WO 9943643

PRIORITY APPLN. INFO: US 1998-55557 19980406; US 1998-30936 19980226; US 2001-765072 20010118

AB WO 9943643 A UPAB: 19991026

NOVELTY - Arylation or vinylation of hydrazines, hydrazones, **hydroxylamines** or oximes involves reaction with an activated compound and a transition metal catalyst. The products are optionally converted into pyrroles, indoles, furans or benzofurans.

DETAILED DESCRIPTION - Synthesis of pyrrole, indole, furan or benzofuran compounds (I) comprises:

(a) reacting a transition metal catalyst, an activated aromatic or vinyl compound (II) and a hydrazine, hydrazone, **hydroxylamine** or oxime compound (III) (or their salts) to form a new carbon-heteroatom bond between the activated carbon of (II) and a heteroatom of (III); and

(b) subjecting the product (IV) to Bronsted or Lewis acidic conditions to form (I).

INDEPENDENT CLAIMS are included:

(i) a method for arylation or vinylation of (III) (or their salts) involving step (a); and

(ii) a method for synthesis of aromatic amines involving transition metal-catalyzed amination of activated aromatic compounds, where the catalyst and ligand are premixed before addition of the remaining reagents.

USE - The process is specifically used (claimed) for preparation of a library of heterocyclic products via parallel, combinatorial synthetic methods; such libraries can be **screened** for **pharmaceutical**, agrochemical or other biological activity. (I) and (IV) are pharmaceuticals and agrochemicals and their intermediates. (IV) can be converted into other heterocycles (e.g. carbazoles), as well as (I).

ADVANTAGE - A wide range of compounds (IV) and (I) can be prepared under mild conditions in high yield. For the amination of aryl halides, combining the transition metal and ligand prior to addition of other reagents enhances the rate of reaction by a factor of 2-6 relative to rates obtained in standard methods, and increases the yield.

Dwg.0/2

L113 ANSWER 40 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1999-494207 [41] WPIDS
DOC. NO. CPI: C1999-144823
TITLE: Use of new and known N-formyl **hydroxylamine** derivatives and their salts for preparing antibacterial compositions.
DERWENT CLASS: B05 C02 C03
INVENTOR(S): BECKETT, R P; CLEMENTS, J M; DAVIES, S J; HUNTER, M G; LAUNCHBURY, S; PRATT, L M; SPAVOLD, Z M; WHITTAKER, M
PATENT ASSIGNEE(S): (BRBI-N) BRITISH BIOTECH PHARM LTD
COUNTRY COUNT: 39
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9939704	A1	19990812	(199941)*	EN	136

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU BR CA CN CZ GB HU IL JP KR MX NO NZ PL RU SG SK TR UA US

AU	9925292	A	19990823	(200005)	
GB	2349884	A	20001115	(200060)	
EP	1052984	A1	20001122	(200061)	EN

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU NL PT SE

NO	2000003969	A	20000928	(200061)	
BR	9907689	A	20001114	(200064)	
ZA	9902045	A	20001227	(200104)#	92
CZ	2000002889	A3	20010117	(200107)	
CN	1298299	A	20010606	(200157)	
KR	2001040621	A	20010515	(200167)	
MX	2000007709	A1	20010401	(200171)	
JP	2002502815	W	20020129	(200211)	164
HU	2001002901	A2	20011228	(200216)	
US	6423690	B1	20020723	(200254)	
AU	749699	B	20020704	(200255)	
US	2002165167	A1	20021107	(200275)	
NZ	505675	A	20021122	(200301)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9939704	A1	WO 1999-GB386	19990205
AU 9925292	A	AU 1999-25292	19990205
GB 2349884	A	WO 1999-GB386	19990205
		GB 2000-16855	20000711
EP 1052984	A1	EP 1999-904977	19990205
		WO 1999-GB386	19990205
NO 2000003969	A	WO 1999-GB386	19990205
		NO 2000-3969	20000804
BR 9907689	A	BR 1999-7689	19990205
		WO 1999-GB386	19990205
ZA 9902045	A	ZA 1999-2045	19990312
CZ 2000002889	A3	WO 1999-GB386	19990205
		CZ 2000-2889	19990205
CN 1298299	A	CN 1999-802752	19990205
KR 2001040621	A	KR 2000-708492	20000803
MX 2000007709	A1	MX 2000-7709	20000807
JP 2002502815	W	WO 1999-GB386	19990205
		JP 2000-530203	19990205
HU 2001002901	A2	WO 1999-GB386	19990205
		HU 2001-2901	19990205
US 6423690	B1	WO 1999-GB386	19990205
		US 2000-355489	20000107
AU 749699	B	AU 1999-25292	19990205
US 2002165167	A1 Div ex	US 2000-355489	20000107
		US 2002-134754	20020430
NZ 505675	A	NZ 1999-505675	19990205
		WO 1999-GB386	19990205

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9925292	A	Based on	WO 9939704
GB 2349884	A	Based on	WO 9939704
EP 1052984	A1	Based on	WO 9939704
BR 9907689	A	Based on	WO 9939704
CZ 2000002889	A3	Based on	WO 9939704
JP 2002502815	W	Based on	WO 9939704
HU 2001002901	A2	Based on	WO 9939704

US 6423690 B1 Based on WO 9939704
AU 749699 B Previous Publ. AU 9925292
Based on WO 9939704
US 2002165167 A1 Div ex US 6423690
NZ 505675 A Div in NZ 521033
Based on WO 9939704

PRIORITY APPLN. INFO: GB 1998-28318 19981222; GB 1998-2549 19980207; GB 1998-6300 19980324; GB 1998-10463 19980516; ZA 1999-2045 19990312

AB WO 9939704 A UPAB: 20010405
NOVELTY - Use of N-formyl **hydroxylamine** derivatives (I) and their salts in the preparation of antibacterial compositions is new.
DETAILED DESCRIPTION - Use of N-formyl **hydroxylamine** derivatives of formula (I) and their salts in the preparation of antibacterial compositions is new.
R1 = H or 1-6C alkyl (optionally substituted by one or more of halo);
R2 = R10-(X)n-(ALK)m;
R10 = H or 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, cycloalkyl, aryl or heteroaryl (all optionally substituted by 1-6C alkyl, 1-6C alkoxy, hydroxy, mercapto, 1-6C alkylthio, amino, halo, trifluoromethyl, cyano, nitro, COOH, CONH2, COORA, NHCORA, NHRA, NRARB or CONRARB);
RA, RB = 1-6C alkyl;
ALK = 1-6C alkylene, 2-6C alkenylene or 2-6C alkynylene (all optionally interrupted by one or more non-adjacent NH, O or S);
X = NH, O or S;
m, n = 0-1;
A = NR5R6 or a group of formula (i)-(iii);
R3 = H;
R4 = side-chain of (non)natural alpha amino acid; or
R3+R4 = optionally substituted, saturated, heterocyclic 5-8-membered ring optionally fused to a carbocyclic or 2nd heterocyclic ring;
R5, R6 = H or optionally substituted 1-8C alkyl, cycloalkyl, aryl, aryl-(1-6C) alkyl, heterocycle or heterocycle-(1-6C) alkyl; or
R5+R6 = an optionally substituted, saturated, 3-8C heterocyclic ring optionally fused to a carbocyclic or 2nd heterocyclic ring; and
R7 = H, 1-6C alkyl or acyl.
INDEPENDENT CLAIMS are also included for:
(1) compounds of formula (I'):
R2' = R10-(ALK)m;
provided that:
(i) when A is group (i) or (ii) and R2 is 2-5C alkyl then R4 is not the side chain of a natural amino acid or the side chain of a natural alpha amino in which any functional substituents are protected, any amino groups are acylated, and any carboxyl groups are esterified:
(ii) when A is group (i) or (ii) then R4 is not a bicyclic arylmethyl group;
(iii) when A is group (i) and R2 is cyclopropyl, cyclobutylmethyl or cyclopentylmethyl and one of R5 and R6 is H, then R4 is not tert-butyl.
(2) antibacterial pharmaceutical or veterinary compositions comprising (I) and a 2nd antibacterial agent together with an excipient or a carrier;
(3) a method for identification of antibacterial compounds;
(4) a method for treating bacterial infections comprising administering (I);
(5) use of a compound which inhibits the activity of bacterial polypeptide deformylase (PDF), in the preparation of an antibacterial composition or agent, provided that:
(i) the compound is not of formula (XI)
(a) R = cyclic amino; W = H, methyl, isopropyl, isobutyl or benzyl;
Y = H, 1-6C alkyl, phenyl, benzyl, 4-chlorophenylmethyl, 4-nitrophenylmethyl or 4-aminophenylmethyl; or
(b) R = 2-pyridylamino or 2-thiazolylamino; W = isopropyl; Y = n

-pentyl; or

(c) R = diethylamino; W = methyl or isopropyl; and Y = n-pentyl; and

(ii) the compound is not one containing a divalent piperazin-1,6-diyl group;

(6) a method for treating bacterial infection or contamination comprising administering to the patient or to the site a compound as in (5).

ACTIVITY - Antibacterial.

Minimal inhibitory concentrations (MIC) of (I) against Escherichia coli strain DH5a, Enterobacter cloacae, Klebsiella pneumoniae and Staphylococcus capitis were determined as follows. Stock solutions of test compounds (1: 2R (or S) ((formyl-hydroxyamino)-methyl)-hexanoic acid -(2,2-dimethyl-1S-methyl-carbamoyl-propyl)-amide, and 2: 2R (or S)-((formyl-hydroxy-amino)-methyl-hexanoic acid-(2,2-dimethyl-1S-tertiary butyl-carbamoyl-propyl)-amide) and three standard laboratory antibiotics (3: carbenicillin, 4: kanamycin, 5: chloramphenicol) were prepared by dissolution of each compound in DMSO (10 mM). Two-fold serial dilutions were prepared in 2xYT broth (tryptone 16 g/l; yeast extract 10 g/l; sodium chloride 5 g/l) to give 0.05 ml compound-containing medium per well. Inoculae were prepared from cultures grown overnight in 2xYT broth at 37 deg. C. Cell densities were adjusted to absorbance at 600 nm (A660) = 0.1, with optical density-standardized preparations diluted 1:1000 in 2xYT broth and each well inoculated with 0.05 ml diluted bacteria. Microtiter plates were incubated at 37 deg. C for 18 hours in a humidified incubator. The MIC (mu M) was recorded as the lowest concentration of drug that inhibited visible growth. The results for the antibiotics were as follows: test compound (1) E. coli DH5 alpha = 12.5, S. capitis = 100, E. cloacae = 50 and K. pneumoniae = 25; test compound (2) E. coli DH5 alpha = 6.25, S. capitis = 25, E. cloacae = 25 and K. pneumoniae = 12.5; standard (3) E. coli DH5 alpha = 25, S. capitis less than 1.56, E. cloacae greater than 200 and K. pneumoniae = 200; standard (4) E. coli DH5 alpha = 3.12, S. capitis 6.25, E. cloacae = 25 and K. pneumoniae = 12.5; and standard (5) E. coli DH5 alpha = 12.5, S. capitis less than 1.56, E. cloacae = 50 and K. pneumoniae = 25.

MECHANISM OF ACTION - Polypeptide deformylase (PDF) inhibitor.

USE - As pharmaceutical or veterinary antibacterial compositions for the treatment of bacterial infections in humans and non-human mammals (claimed). Active against a range of Gram-negative and positive organisms including those resistant to commonly used antibiotics such as vancomycin and beta -lactam antibiotics e.g. methicillin-resistant Staphylococcus aureus. Used for identification of antibacterial compounds and to treat bacterial infection or contamination (claimed).

Dwg.0/0

L113 ANSWER 41 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1998-348070 [30] WPIDS
DOC. NO. CPI: C1998-107523
TITLE: New library comprising **hydroxylamine** and/or **hydroxylamine** derivative **compounds** - useful for **screening** for biological activity; particularly inhibition of metallo-protease(s).
DERWENT CLASS: A96 B05 E19
INVENTOR(S): NHU, K; PATEL, D; NGU, K; PATEL, D V
PATENT ASSIGNEE(S): (VERS-N) VERSICOR INC; (NGUK-I) NGU K; (PATE-I) PATEL D V
COUNTRY COUNT: 77
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9818754	A1	19980507	(199830)*	EN	98

RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU

IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO
NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9854263 A 19980522 (199840)
US 6281245 B1 20010828 (200151)
US 2001053555 A1 20011220 (200206)
US 6541276 B2 20030401 (200324)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9818754	A1		WO 1997-US19481	19971027
AU 9854263	A		AU 1998-54263	19971027
US 6281245	B1	Provisional	US 1996-29788P	19961028
		Provisional	US 1997-47468P	19970523
		CIP of	US 1997-958638	19971027
			US 1998-74035	19980506
US 2001053555	A1	Provisional	US 1996-29788P	19961028
		Provisional	US 1997-47468P	19970523
			US 1997-958638	19971027
US 6541276	B2	Provisional	US 1996-29788P	19961028
		Provisional	US 1997-47468P	19970523
			US 1997-958638	19971027

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9854263	A	Based on	WO 9818754

PRIORITY APPLN. INFO: US 1997-47468P 19970523; US 1996-29788P 19961028; US 1997-958638 19971027; US 1998-74035 19980506

AB WO 9818754 A UPAB: 19980730
New library comprising **hydroxylamine** and/or **hydroxylamine** derivative compounds is prepared by preparing derivatising a solid support bound alkoxyamine; cleaving the derivatised alkoxyamines from the solid support and removing the alkoxy protecting group. The library particularly comprises at least 40 compounds. Also claimed are (1) an O-protected **hydroxylamine** functionalised resin for the preparation of a library containing **hydroxylamine** and/or **hydroxylamine** derivative compounds; (2) compounds of formula (I). b = 1-5; J = OH or NH-RESIN; Q = S or T; S = bromide, iodide, mesylate, tosylate or p-nitrophenylsulphonate; T = NHOP1; P1 = 2-tetrahydropyranyl, trityl, t-butyldimethylsilyl, allyl, benzyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl; RESIN = solid or polymeric support; (3) an O-protected **hydroxylamine**-linker compound for attachment to an amine-bearing resin, comprising a cleavable linker group and an O-protected **hydroxylamine**, the linker group being acid-labile or photolabile and (4) a derivatised resin comprising hydroxymethylphenoxy resin or 2-methoxy-4-alkoxybenzyl alcohol resin, with the active hydroxyl group of the resin replaced by a leaving group comprising bromide, iodide, mesylate, tosylate or p-nitrophenylsulphonate.
Preferably, the step of preparing a solid support-bound alkoxyamine comprises adding an alkoxylamine nucleophile comprising an alkoxy protecting group to a solid support comprising a leaving group, thereby displacing the leaving group from the solid support to produce a solid support-bound alkoxyamine. The leaving group is preferably bromide, iodide or mesylate. The solid support comprising a leaving group is preferably bromomethylphenoxy resin. Alternatively the step of preparing a solid support-bound alkoxyamine comprises adding an alkoxy-protected **hydroxylamine**-linker intermediate comprising an O-protected alkoxyamine and a linker group to a solid support bearing an amine group

to produce a solid support-bound alkoxyamine. The solid support bound alkoxyamine is the O-protected **hydroxylamine** functionalised resin. The active hydroxyl group of the derivatised resin is replaced with bromide or iodide.

USE - The library is used for **screening** **hydroxylamine** and/or **hydroxylamine** derivative **compounds** which have biological activity e.g. inhibition of metalloproteases or specific interaction with a targetted enzyme or receptor important in the modulation of a disease including tumour growth and angiogenesis, arthritis, connective tissue disorders, inflammatory diseases and retinopathies. The compounds can be administered orally, topically, nasally, parenterally, rectally or vaginally or applied to the skin and mucous membranes, as prodrugs or in liposome formulations. Dwg.0/10

L113 ANSWER 42 OF 42 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1996-433389 [43] WPIDS
DOC. NO. CPI: C1996-135938
TITLE: Prepn. of hydroxamic acids as metallo-proteinase inhibitors - uses solid phase of modified resin carrying **hydroxylamine** gps. allowing sequential synthesis to be performed in high yield with min. purification.
DERWENT CLASS: A14 A96 B04 B05
INVENTOR(S): FLOYD, C D; LEWIS, C N
PATENT ASSIGNEE(S): (BRBI-N) BRITISH BIOTECH PHARM LTD
COUNTRY COUNT: 19
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9626223	A1	19960829	(199643)*	EN	47
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: JP US					
EP 811019	A1	19971210	(199803)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE					
JP 11500620	W	19990119	(199913)		50
EP 811019	B1	19990407	(199918)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE					
DE 69602016	E	19990512	(199925)		
US 5932695	A	19990803	(199937)		
US 6093798	A	20000725	(200038)		
US 6228988	B1	20010508	(200128)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9626223	A1		WO 1996-GB428	19960226
EP 811019	A1		EP 1996-903152	19960226
			WO 1996-GB428	19960226
JP 11500620	W		JP 1996-525514	19960226
			WO 1996-GB428	19960226
EP 811019	B1		EP 1996-903152	19960226
			WO 1996-GB428	19960226
DE 69602016	E		DE 1996-602016	19960226
			EP 1996-903152	19960226
			WO 1996-GB428	19960226
US 5932695	A		WO 1996-GB428	19960226
			US 1997-809499	19970324
US 6093798	A	Div ex	WO 1996-GB428	19960226
		Div ex	US 1997-809499	19970324
			US 1999-328492	19990609
US 6228988	B1	Cont of	WO 1996-GB428	19960226

Div ex	US 1997-809499	19970324
	US 1999-328493	19990609

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 811019	A1	Based on	WO 9626223
JP 11500620	W	Based on	WO 9626223
EP 811019	B1	Based on	WO 9626223
DE 69602016	E	Based on	EP 811019
		Based on	WO 9626223
US 5932695	A	Based on	WO 9626223
~~US 6228988~~	B1	Div ex	US 5932695

PRIORITY APPLN. INFO: GB 1995-3749 19950224

AB WO 9626223 A UPAB: 19990416

Solid-phase reaction component (I) comprises a solid substrate, insoluble in aq. or organic reaction media, carrying a plurality of covalently bound opt. protected **hydroxylamine** gps. of formula (i) or (ii). P1 = H or amino protecting gp.; P2 = H or OH protecting gp; and (a) = a covalent bond, cleavable by acid or photolysis, which links (i) or (ii) to the residue of (I).

USE - (I) are useful in the prepn. of hydroxamic acid derivs. for use as inhibitors of zinc metalloproteinase enzymes responsible for tissue degradation and the release of tumour necrosis factor from cells.

ADVANTAGE - Use of (I) provides a convenient method for syntheses involving several stages, facilitating the purification and recovery of prods.. The ease of handling makes batch prepn. or prepn. of combinatorial libraries of cpds. possible to allow faster prepn. and **screening** of potentially active **cpds**..

Dwg.0/0

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=> fil capl; d que 129; d que 132
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FILE COVERS 1907 - 30 May 2003 VOL 138 ISS 23
FILE LAST UPDATED: 29 May 2003 (20030529/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

L5 128 SEA FILE=REGISTRY ABB=ON (622-30-0/BI OR 113236-14-9/BI OR 113768-54-0/BI OR 115750-71-5/BI OR 115750-72-6/BI OR 116250-34-1/BI OR 136580-41-1/BI OR 13782-57-5/BI OR 141218-23-7/BI OR 14469-03-5/BI OR 154441-65-3/BI OR 16649-50-6/BI OR 171095-30-0/BI OR 179076-85-8/BI OR 206537-23-7/BI OR 216445-62-4/BI OR 2211-64-5/BI OR 223118-54-5/BI OR 250215-06-6/BI OR 25100-12-3/BI OR 25316-40-9/BI OR 26228-72-8/BI OR 27886-24-4/BI OR 29072-73-9/BI OR 2912-93-8/BI OR 2912-94-9/BI OR 2912-95-0/BI OR 2912-97-2/BI OR 30635-68-8/BI OR 30718-86-6/BI OR 3376-24-7/BI OR 337905-17-6/BI OR 337905-18-7/BI OR 337905-19-8/BI OR 337905-20-1/BI OR 337905-21-2/BI OR 337905-22-3/BI OR 337905-23-4/BI OR 337905-24-5/BI OR 337905-25-6/BI OR 337905-26-7/BI OR 337905-27-8/BI OR 337905-28-9/BI OR 337905-29-0/BI OR 337905-30-3/BI OR 337905-31-4/BI OR 337905-32-5/BI OR 337905-33-6/BI OR 337905-34-7/BI OR 337905-35-8/BI OR 337905-36-9/BI OR 337905-37-0/BI OR 337905-38-1/BI OR 337905-39-2/BI OR 337905-40-5/BI OR 337905-41-6/BI OR 337905-42-7/BI OR 337905-43-8/BI OR 337905-44-9/BI OR 337905-45-0/BI OR 337905-46-1/BI OR 337905-47-2/BI OR 337905-48-3/BI OR 337905-49-4/BI OR 337905-50-7/BI OR 337905-51-8/BI OR 337905-52-9/BI OR 337905-53-0/BI OR 337905-54-1/BI OR 337905-55-2/BI OR 337905-56-3/BI OR 337905-57-4/BI OR 337905-58-5/BI OR 337905-59-6/BI OR 337905-60-9/BI OR 337905-61-0/BI OR 337905-62-1/BI OR 337905-63-2/BI OR 337905-64-3/BI OR 337905-65-4/BI OR 337905-66-5/BI OR 337905-67-6/BI OR 337905-68-7/BI OR 337905-69-8/BI OR 337905-70-1/BI OR 337905-71-2/BI OR 337905-72-3/BI OR 337905-73-4/BI OR 337905-74-5/BI OR 337905-75-6/BI OR 337905-76-7/BI OR 337905-77-8/BI OR 337905-78-9/BI OR 337905-79-0/BI OR 337905-80-3/BI OR 337905-81-4/BI OR 337905-82-5/BI OR 337905-83-6/BI OR 337964-36-0/BI OR 337964-37-1/BI
L9 7584 SEA FILE=CAPLUS ABB=ON (CELL? OR REPLICATIVE)(3A)(AGING OR SENESCENCE)/OBI
L10 23516 SEA FILE=CAPLUS ABB=ON OXIDATIVE(2A)(STRESS? OR DAMAG?)/OBI
L19 1 SEA FILE=REGISTRY ABB=ON 593-77-1
L20 1 SEA FILE=REGISTRY ABB=ON 622-30-0
L21 1 SEA FILE=REGISTRY ABB=ON 16649-50-6
L22 603 SEA FILE=REGISTRY ABB=ON C8H8N2O2/MF
L23 115 SEA FILE=REGISTRY ABB=ON C4H11NO/MF

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L24           1 SEA FILE=REGISTRY ABB=ON  L5 AND L22
L25           3 SEA FILE=REGISTRY ABB=ON  L5 AND L23
L26           1 SEA FILE=REGISTRY ABB=ON  1-BUTANAMINE AND L25
L28         959 SEA FILE=CAPLUS ABB=ON  (L19 OR L20 OR L21) OR L24 OR L26
L29           9 SEA FILE=CAPLUS ABB=ON  (L9 OR L10) AND L28


L5          128 SEA FILE=REGISTRY ABB=ON  (622-30-0/BI OR 113236-14-9/BI OR
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                14469-03-5/BI OR 154441-65-3/BI OR 16649-50-6/BI OR 171095-30-0
                /BI OR 179076-85-8/BI OR 206537-23-7/BI OR 216445-62-4/BI OR
                2211-64-5/BI OR 223118-54-5/BI OR 250215-06-6/BI OR 25100-12-3/
                BI OR 25316-40-9/BI OR 26228-72-8/BI OR 27886-24-4/BI OR
                29072-73-9/BI OR 2912-93-8/BI OR 2912-94-9/BI OR 2912-95-0/BI
                OR 2912-97-2/BI OR 30635-68-8/BI OR 30718-86-6/BI OR 3376-24-7/
                BI OR 337905-17-6/BI OR 337905-18-7/BI OR 337905-19-8/BI OR
                337905-20-1/BI OR 337905-21-2/BI OR 337905-22-3/BI OR 337905-23
                -4/BI OR 337905-24-5/BI OR 337905-25-6/BI OR 337905-26-7/BI OR
                337905-27-8/BI OR 337905-28-9/BI OR 337905-29-0/BI OR 337905-30
                -3/BI OR 337905-31-4/BI OR 337905-32-5/BI OR 337905-33-6/BI OR
                337905-34-7/BI OR 337905-35-8/BI OR 337905-36-9/BI OR 337905-37
                -0/BI OR 337905-38-1/BI OR 337905-39-2/BI OR 337905-40-5/BI OR
                337905-41-6/BI OR 337905-42-7/BI OR 337905-43-8/BI OR 337905-44
                -9/BI OR 337905-45-0/BI OR 337905-46-1/BI OR 337905-47-2/BI OR
                337905-48-3/BI OR 337905-49-4/BI OR 337905-50-7/BI OR 337905-51
                -8/BI OR 337905-52-9/BI OR 337905-53-0/BI OR 337905-54-1/BI OR
                337905-55-2/BI OR 337905-56-3/BI OR 337905-57-4/BI OR 337905-58
                -5/BI OR 337905-59-6/BI OR 337905-60-9/BI OR 337905-61-0/BI OR
                337905-62-1/BI OR 337905-63-2/BI OR 337905-64-3/BI OR 337905-65
                -4/BI OR 337905-66-5/BI OR 337905-67-6/BI OR 337905-68-7/BI OR
                337905-69-8/BI OR 337905-70-1/BI OR 337905-71-2/BI OR 337905-72
                -3/BI OR 337905-73-4/BI OR 337905-74-5/BI OR 337905-75-6/BI OR
                337905-76-7/BI OR 337905-77-8/BI OR 337905-78-9/BI OR 337905-79
                -0/BI OR 337905-80-3/BI OR 337905-81-4/BI OR 337905-82-5/BI OR
                337905-83-6/BI OR 337964-36-0/BI OR 337964-37-1/BI
L19           1 SEA FILE=REGISTRY ABB=ON  593-77-1
L20           1 SEA FILE=REGISTRY ABB=ON  622-30-0
L21           1 SEA FILE=REGISTRY ABB=ON  16649-50-6
L22         603 SEA FILE=REGISTRY ABB=ON  C8H8N2O2/MF
L23         115 SEA FILE=REGISTRY ABB=ON  C4H11NO/MF
L24           1 SEA FILE=REGISTRY ABB=ON  L5 AND L22
L25           3 SEA FILE=REGISTRY ABB=ON  L5 AND L23
L26           1 SEA FILE=REGISTRY ABB=ON  1-BUTANAMINE AND L25
L28         959 SEA FILE=CAPLUS ABB=ON  (L19 OR L20 OR L21) OR L24 OR L26
L30       28630 SEA FILE=CAPLUS ABB=ON  SCREENING/CW
L32           2 SEA FILE=CAPLUS ABB=ON  L28 AND L30

=> s (l29 or l32) not l110

L114          7 (L29 OR L32) NOT L110
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previously printed

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=> fil medl; d que l56; d que l57

FILE 'MEDLINE' ENTERED AT 16:39:12 ON 30 MAY 2003

 FILE LAST UPDATED: 29 MAY 2003 (20030529/UP).  FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
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MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L5 128 SEA FILE=REGISTRY ABB=ON (622-30-0/BI OR 113236-14-9/BI OR 113768-54-0/BI OR 115750-71-5/BI OR 115750-72-6/BI OR 116250-34-1/BI OR 136580-41-1/BI OR 13782-57-5/BI OR 141218-23-7/BI OR 14469-03-5/BI OR 154441-65-3/BI OR 16649-50-6/BI OR 171095-30-0/BI OR 179076-85-8/BI OR 206537-23-7/BI OR 216445-62-4/BI OR 2211-64-5/BI OR 223118-54-5/BI OR 250215-06-6/BI OR 25100-12-3/BI OR 25316-40-9/BI OR 26228-72-8/BI OR 27886-24-4/BI OR 29072-73-9/BI OR 2912-93-8/BI OR 2912-94-9/BI OR 2912-95-0/BI OR 2912-97-2/BI OR 30635-68-8/BI OR 30718-86-6/BI OR 3376-24-7/BI OR 337905-17-6/BI OR 337905-18-7/BI OR 337905-19-8/BI OR 337905-20-1/BI OR 337905-21-2/BI OR 337905-22-3/BI OR 337905-23-4/BI OR 337905-24-5/BI OR 337905-25-6/BI OR 337905-26-7/BI OR 337905-27-8/BI OR 337905-28-9/BI OR 337905-29-0/BI OR 337905-30-3/BI OR 337905-31-4/BI OR 337905-32-5/BI OR 337905-33-6/BI OR 337905-34-7/BI OR 337905-35-8/BI OR 337905-36-9/BI OR 337905-37-0/BI OR 337905-38-1/BI OR 337905-39-2/BI OR 337905-40-5/BI OR 337905-41-6/BI OR 337905-42-7/BI OR 337905-43-8/BI OR 337905-44-9/BI OR 337905-45-0/BI OR 337905-46-1/BI OR 337905-47-2/BI OR 337905-48-3/BI OR 337905-49-4/BI OR 337905-50-7/BI OR 337905-51-8/BI OR 337905-52-9/BI OR 337905-53-0/BI OR 337905-54-1/BI OR 337905-55-2/BI OR 337905-56-3/BI OR 337905-57-4/BI OR 337905-58-5/BI OR 337905-59-6/BI OR 337905-60-9/BI OR 337905-61-0/BI OR 337905-62-1/BI OR 337905-63-2/BI OR 337905-64-3/BI OR 337905-65-4/BI OR 337905-66-5/BI OR 337905-67-6/BI OR 337905-68-7/BI OR 337905-69-8/BI OR 337905-70-1/BI OR 337905-71-2/BI OR 337905-72-3/BI OR 337905-73-4/BI OR 337905-74-5/BI OR 337905-75-6/BI OR 337905-76-7/BI OR 337905-77-8/BI OR 337905-78-9/BI OR 337905-79-0/BI OR 337905-80-3/BI OR 337905-81-4/BI OR 337905-82-5/BI OR 337905-83-6/BI OR 337964-36-0/BI OR 337964-37-1/BI
L19 1 SEA FILE=REGISTRY ABB=ON 593-77-1
L20 1 SEA FILE=REGISTRY ABB=ON 622-30-0
L21 1 SEA FILE=REGISTRY ABB=ON 16649-50-6
L22 603 SEA FILE=REGISTRY ABB=ON C8H8N2O2/MF
L23 115 SEA FILE=REGISTRY ABB=ON C4H11NO/MF
L24 1 SEA FILE=REGISTRY ABB=ON L5 AND L22
L25 3 SEA FILE=REGISTRY ABB=ON L5 AND L23
L26 1 SEA FILE=REGISTRY ABB=ON 1-BUTANAMINE AND L25
L41 73602 SEA FILE=MEDLINE ABB=ON DRUG EVALUATION, PRECLINICAL+NT/CT
L55 16 SEA FILE=MEDLINE ABB=ON (L19 OR L20 OR L21) OR L24 OR L26
L56 0 SEA FILE=MEDLINE ABB=ON L55 AND L41

L5 128 SEA FILE=REGISTRY ABB=ON (622-30-0/BI OR 113236-14-9/BI OR 113768-54-0/BI OR 115750-71-5/BI OR 115750-72-6/BI OR 116250-34-1/BI OR 136580-41-1/BI OR 13782-57-5/BI OR 141218-23-7/BI OR 14469-03-5/BI OR 154441-65-3/BI OR 16649-50-6/BI OR 171095-30-0/BI OR 179076-85-8/BI OR 206537-23-7/BI OR 216445-62-4/BI OR 2211-64-5/BI OR 223118-54-5/BI OR 250215-06-6/BI OR 25100-12-3/BI OR 25316-40-9/BI OR 26228-72-8/BI OR 27886-24-4/BI OR 29072-73-9/BI OR 2912-93-8/BI OR 2912-94-9/BI OR 2912-95-0/BI OR 2912-97-2/BI OR 30635-68-8/BI OR 30718-86-6/BI OR 3376-24-7/BI OR 337905-17-6/BI OR 337905-18-7/BI OR 337905-19-8/BI OR 337905-20-1/BI OR 337905-21-2/BI OR 337905-22-3/BI OR 337905-23-4/BI OR 337905-24-5/BI OR 337905-25-6/BI OR 337905-26-7/BI OR 337905-27-8/BI OR 337905-28-9/BI OR 337905-29-0/BI OR 337905-30

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                -3/BI OR 337905-31-4/BI OR 337905-32-5/BI OR 337905-33-6/BI OR
                337905-34-7/BI OR 337905-35-8/BI OR 337905-36-9/BI OR 337905-37
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                337905-41-6/BI OR 337905-42-7/BI OR 337905-43-8/BI OR 337905-44
                -9/BI OR 337905-45-0/BI OR 337905-46-1/BI OR 337905-47-2/BI OR
                337905-48-3/BI OR 337905-49-4/BI OR 337905-50-7/BI OR 337905-51
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                337905-55-2/BI OR 337905-56-3/BI OR 337905-57-4/BI OR 337905-58
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                337905-62-1/BI OR 337905-63-2/BI OR 337905-64-3/BI OR 337905-65
                -4/BI OR 337905-66-5/BI OR 337905-67-6/BI OR 337905-68-7/BI OR
                337905-69-8/BI OR 337905-70-1/BI OR 337905-71-2/BI OR 337905-72
                -3/BI OR 337905-73-4/BI OR 337905-74-5/BI OR 337905-75-6/BI OR
                337905-76-7/BI OR 337905-77-8/BI OR 337905-78-9/BI OR 337905-79
                -0/BI OR 337905-80-3/BI OR 337905-81-4/BI OR 337905-82-5/BI OR
                337905-83-6/BI OR 337964-36-0/BI OR 337964-37-1/BI
L19             1 SEA FILE=REGISTRY ABB=ON  593-77-1
L20             1 SEA FILE=REGISTRY ABB=ON  622-30-0
L21             1 SEA FILE=REGISTRY ABB=ON  16649-50-6
L22           603 SEA FILE=REGISTRY ABB=ON  C8H8N2O2/MF
L23           115 SEA FILE=REGISTRY ABB=ON  C4H11NO/MF
L24             1 SEA FILE=REGISTRY ABB=ON  L5 AND L22
L25             3 SEA FILE=REGISTRY ABB=ON  L5 AND L23
L26             1 SEA FILE=REGISTRY ABB=ON  1-BUTANAMINE AND L25
L43          6846 SEA FILE=MEDLINE ABB=ON  CELL AGING+NT/CT
L45         13449 SEA FILE=MEDLINE ABB=ON  OXIDATIVE STRESS/CT
L55            16 SEA FILE=MEDLINE ABB=ON  (L19 OR L20 OR L21) OR L24 OR L26
L57             3 SEA FILE=MEDLINE ABB=ON  L55 AND (L43 OR L45)


=> fil wpids; d que l82; d que l84

FILE 'WPIDS' ENTERED AT 16:39:12 ON 30 MAY 2003
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FILE LAST UPDATED:         29 MAY 2003      <20030529/UP>
MOST RECENT DERWENT UPDATE:     200334       <200334/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS  <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L67           750 SEA FILE=WPIDS ABB=ON  OXIDATIVE?(2A)(DAMAG? OR STRESS?)
L68          1186 SEA FILE=WPIDS ABB=ON  (CELL? OR REPLICATIVE)(3A)(AGING OR
                  SENESCENCE OR SURVIVAL)
L77            57 SEA FILE=WPIDS ABB=ON  METHYLHYDROXYLAMINE
L78             1 SEA FILE=WPIDS ABB=ON  N-BUTYLHYDROXYLAMINE
L79             2 SEA FILE=WPIDS ABB=ON  TERTBUTYLHYDROXYLAMINE
L80            14 SEA FILE=WPIDS ABB=ON  BENZYLHYDROXYLAMINE
L81            74 SEA FILE=WPIDS ABB=ON  (METHYL OR BUTYL OR TERTBUTYL OR
```

BENZYL)(W)(HYDROXYLAMINE OR HYDROXYL AMINE)
L82 3 SEA FILE=WPIDS ABB=ON (L77 OR L78 OR L79 OR L80 OR L81) AND (L67 OR L68)

L69 223506 SEA FILE=WPIDS ABB=ON SCREEN?
L77 57 SEA FILE=WPIDS ABB=ON METHYLHYDROXYLAMINE
L78 1 SEA FILE=WPIDS ABB=ON N-BUTYLHYDROXYLAMINE
L79 2 SEA FILE=WPIDS ABB=ON TERTBUTYLHYDROXYLAMINE
L80 14 SEA FILE=WPIDS ABB=ON BENZYLHYDROXYLAMINE
L81 74 SEA FILE=WPIDS ABB=ON (METHYL OR BUTYL OR TERTBUTYL OR BENZYL)(W)(HYDROXYLAMINE OR HYDROXYL AMINE)
L84 0 SEA FILE=WPIDS ABB=ON (L77 OR L78 OR L79 OR L80 OR L81) AND L69

=> s l82 not l112

L115 3 L82 NOT (L112) previously printed

=> fil embase; d que l98

FILE 'EMBASE' ENTERED AT 16:39:14 ON 30 MAY 2003

FILE COVERS 1974 TO 29 May 2003 (20030529/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L5 128 SEA FILE=REGISTRY ABB=ON (622-30-0/BI OR 113236-14-9/BI OR 113768-54-0/BI OR 115750-71-5/BI OR 115750-72-6/BI OR 116250-34-1/BI OR 136580-41-1/BI OR 13782-57-5/BI OR 141218-23-7/BI OR 14469-03-5/BI OR 154441-65-3/BI OR 16649-50-6/BI OR 171095-30-0/BI OR 179076-85-8/BI OR 206537-23-7/BI OR 216445-62-4/BI OR 2211-64-5/BI OR 223118-54-5/BI OR 250215-06-6/BI OR 25100-12-3/BI OR 25316-40-9/BI OR 26228-72-8/BI OR 27886-24-4/BI OR 29072-73-9/BI OR 2912-93-8/BI OR 2912-94-9/BI OR 2912-95-0/BI OR 2912-97-2/BI OR 30635-68-8/BI OR 30718-86-6/BI OR 3376-24-7/BI OR 337905-17-6/BI OR 337905-18-7/BI OR 337905-19-8/BI OR 337905-20-1/BI OR 337905-21-2/BI OR 337905-22-3/BI OR 337905-23-4/BI OR 337905-24-5/BI OR 337905-25-6/BI OR 337905-26-7/BI OR 337905-27-8/BI OR 337905-28-9/BI OR 337905-29-0/BI OR 337905-30-3/BI OR 337905-31-4/BI OR 337905-32-5/BI OR 337905-33-6/BI OR 337905-34-7/BI OR 337905-35-8/BI OR 337905-36-9/BI OR 337905-37-0/BI OR 337905-38-1/BI OR 337905-39-2/BI OR 337905-40-5/BI OR 337905-41-6/BI OR 337905-42-7/BI OR 337905-43-8/BI OR 337905-44-9/BI OR 337905-45-0/BI OR 337905-46-1/BI OR 337905-47-2/BI OR 337905-48-3/BI OR 337905-49-4/BI OR 337905-50-7/BI OR 337905-51-8/BI OR 337905-52-9/BI OR 337905-53-0/BI OR 337905-54-1/BI OR 337905-55-2/BI OR 337905-56-3/BI OR 337905-57-4/BI OR 337905-58-5/BI OR 337905-59-6/BI OR 337905-60-9/BI OR 337905-61-0/BI OR 337905-62-1/BI OR 337905-63-2/BI OR 337905-64-3/BI OR 337905-65-4/BI OR 337905-66-5/BI OR 337905-67-6/BI OR 337905-68-7/BI OR 337905-69-8/BI OR 337905-70-1/BI OR 337905-71-2/BI OR 337905-72-3/BI OR 337905-73-4/BI OR 337905-74-5/BI OR 337905-75-6/BI OR 337905-76-7/BI OR 337905-77-8/BI OR 337905-78-9/BI OR 337905-79-0/BI OR 337905-80-3/BI OR 337905-81-4/BI OR 337905-82-5/BI OR 337905-83-6/BI OR 337964-36-0/BI OR 337964-37-1/BI

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L19           1 SEA FILE=REGISTRY ABB=ON  593-77-1
L20           1 SEA FILE=REGISTRY ABB=ON  622-30-0
L21           1 SEA FILE=REGISTRY ABB=ON  16649-50-6
L22         603 SEA FILE=REGISTRY ABB=ON  C8H8N2O2/MF
L23         115 SEA FILE=REGISTRY ABB=ON  C4H11NO/MF
L24           1 SEA FILE=REGISTRY ABB=ON  L5 AND L22
L25           3 SEA FILE=REGISTRY ABB=ON  L5 AND L23
L26           1 SEA FILE=REGISTRY ABB=ON  1-BUTANAMINE AND L25
L86        2631 SEA FILE=EMBASE ABB=ON  CELL AGING/CT OR "CELL AGING, CELL
               DEGENERATION AND CELL SURVIVAL"/CT
L87       23619 SEA FILE=EMBASE ABB=ON  OXIDATIVE STRESS/CT
L89        9083 SEA FILE=EMBASE ABB=ON  CELL PROTECTION/CT
L90       11148 SEA FILE=EMBASE ABB=ON  ANTIOXIDANT ACTIVITY/CT
L92       62888 SEA FILE=EMBASE ABB=ON  DRUG SCREENING/CT
L95      224106 SEA FILE=EMBASE ABB=ON  CELL CULTURE+NT/CT
L97          15 SEA FILE=EMBASE ABB=ON  (L19 OR L20 OR L21) OR L24 OR L26
L98           0 SEA FILE=EMBASE ABB=ON  L97 AND (L86 OR L87 OR L89 OR L90 OR
               L92 OR L95)


=> fil DRUGU, BIOTECHNO, CABA, IPA, BIOSIS, TOXCENTER, ANABSTR

FILE 'DRUGU' ENTERED AT 16:39:15 ON 30 MAY 2003
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FILE 'IPA' ENTERED AT 16:39:15 ON 30 MAY 2003
COPYRIGHT (C) 2003 American Society of Hospital Pharmacists (ASHP)

FILE 'BIOSIS' ENTERED AT 16:39:15 ON 30 MAY 2003
COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'TOXCENTER' ENTERED AT 16:39:15 ON 30 MAY 2003
COPYRIGHT (C) 2003 ACS

FILE 'ANABSTR' ENTERED AT 16:39:15 ON 30 MAY 2003
COPYRIGHT (c) 2003 THE ROYAL SOCIETY OF CHEMISTRY (RSC)

=> d que l104; d que l106; s (l104 or l106) not l109

L5          128 SEA FILE=REGISTRY ABB=ON  (622-30-0/BI OR 113236-14-9/BI OR
                113768-54-0/BI OR 115750-71-5/BI OR 115750-72-6/BI OR 116250-34
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                /BI OR 179076-85-8/BI OR 206537-23-7/BI OR 216445-62-4/BI OR
                2211-64-5/BI OR 223118-54-5/BI OR 250215-06-6/BI OR 25100-12-3/
                BI OR 25316-40-9/BI OR 26228-72-8/BI OR 27886-24-4/BI OR
                29072-73-9/BI OR 2912-93-8/BI OR 2912-94-9/BI OR 2912-95-0/BI
                OR 2912-97-2/BI OR 30635-68-8/BI OR 30718-86-6/BI OR 3376-24-7/
                BI OR 337905-17-6/BI OR 337905-18-7/BI OR 337905-19-8/BI OR
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337905-48-3/BI OR 337905-49-4/BI OR 337905-50-7/BI OR 337905-51
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337905-69-8/BI OR 337905-70-1/BI OR 337905-71-2/BI OR 337905-72
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337905-76-7/BI OR 337905-77-8/BI OR 337905-78-9/BI OR 337905-79
-0/BI OR 337905-80-3/BI OR 337905-81-4/BI OR 337905-82-5/BI OR
337905-83-6/BI OR 337964-36-0/BI OR 337964-37-1/BI

L19 1 SEA FILE=REGISTRY ABB=ON 593-77-1
L20 1 SEA FILE=REGISTRY ABB=ON 622-30-0
L21 1 SEA FILE=REGISTRY ABB=ON 16649-50-6
L22 603 SEA FILE=REGISTRY ABB=ON C8H8N2O2/MF
L23 115 SEA FILE=REGISTRY ABB=ON C4H11NO/MF
L24 1 SEA FILE=REGISTRY ABB=ON L5 AND L22
L25 3 SEA FILE=REGISTRY ABB=ON L5 AND L23
L26 1 SEA FILE=REGISTRY ABB=ON 1-BUTANAMINE AND L25
L99 166 SEA (L19 OR L20 OR L21) OR L24 OR L26
L100 134424 SEA (CELL? OR REPLICATIVE)(3A)(AGING OR SENESCENCE OR SURVIVAL
OR PROTECT?)
L101 88900 SEA OXIDATIVE?(2A)(STRESS? OR DAMAG?)
L102 137290 SEA ANTIOXIDANT#
L104 19 SEA L99 AND (L100 OR L101 OR L102)

L5 128 SEA FILE=REGISTRY ABB=ON (622-30-0/BI OR 113236-14-9/BI OR
113768-54-0/BI OR 115750-71-5/BI OR 115750-72-6/BI OR 116250-34
-1/BI OR 136580-41-1/BI OR 13782-57-5/BI OR 141218-23-7/BI OR
14469-03-5/BI OR 154441-65-3/BI OR 16649-50-6/BI OR 171095-30-0
/BI OR 179076-85-8/BI OR 206537-23-7/BI OR 216445-62-4/BI OR
2211-64-5/BI OR 223118-54-5/BI OR 250215-06-6/BI OR 25100-12-3/
BI OR 25316-40-9/BI OR 26228-72-8/BI OR 27886-24-4/BI OR
29072-73-9/BI OR 2912-93-8/BI OR 2912-94-9/BI OR 2912-95-0/BI
OR 2912-97-2/BI OR 30635-68-8/BI OR 30718-86-6/BI OR 3376-24-7/
BI OR 337905-17-6/BI OR 337905-18-7/BI OR 337905-19-8/BI OR
337905-20-1/BI OR 337905-21-2/BI OR 337905-22-3/BI OR 337905-23
-4/BI OR 337905-24-5/BI OR 337905-25-6/BI OR 337905-26-7/BI OR
337905-27-8/BI OR 337905-28-9/BI OR 337905-29-0/BI OR 337905-30
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337905-34-7/BI OR 337905-35-8/BI OR 337905-36-9/BI OR 337905-37
-0/BI OR 337905-38-1/BI OR 337905-39-2/BI OR 337905-40-5/BI OR
337905-41-6/BI OR 337905-42-7/BI OR 337905-43-8/BI OR 337905-44
-9/BI OR 337905-45-0/BI OR 337905-46-1/BI OR 337905-47-2/BI OR
337905-48-3/BI OR 337905-49-4/BI OR 337905-50-7/BI OR 337905-51
-8/BI OR 337905-52-9/BI OR 337905-53-0/BI OR 337905-54-1/BI OR
337905-55-2/BI OR 337905-56-3/BI OR 337905-57-4/BI OR 337905-58
-5/BI OR 337905-59-6/BI OR 337905-60-9/BI OR 337905-61-0/BI OR
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-4/BI OR 337905-66-5/BI OR 337905-67-6/BI OR 337905-68-7/BI OR
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-3/BI OR 337905-73-4/BI OR 337905-74-5/BI OR 337905-75-6/BI OR
337905-76-7/BI OR 337905-77-8/BI OR 337905-78-9/BI OR 337905-79
-0/BI OR 337905-80-3/BI OR 337905-81-4/BI OR 337905-82-5/BI OR
337905-83-6/BI OR 337964-36-0/BI OR 337964-37-1/BI

L19 1 SEA FILE=REGISTRY ABB=ON 593-77-1
L20 1 SEA FILE=REGISTRY ABB=ON 622-30-0
L21 1 SEA FILE=REGISTRY ABB=ON 16649-50-6
L22 603 SEA FILE=REGISTRY ABB=ON C8H8N2O2/MF
L23 115 SEA FILE=REGISTRY ABB=ON C4H11NO/MF
L24 1 SEA FILE=REGISTRY ABB=ON L5 AND L22

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L25             3 SEA FILE=REGISTRY ABB=ON  L5 AND L23
L26             1 SEA FILE=REGISTRY ABB=ON  1-BUTANAMINE AND L25
L99           166 SEA (L19 OR L20 OR L21) OR L24 OR L26
L103       229308 SEA (SCREEN? OR EVALUAT? OR TEST?)(3A)(DRUG# OR PHARMACEUT? OR
                  COMPOUND# OR THERAP?)
L106            1 SEA L103 AND L99


L116           18 (L104 OR L106) NOT (L109) previously printed

=> dup rem l57,l114,l116,l115
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PROCESSING COMPLETED FOR L116
PROCESSING COMPLETED FOR L115
L117           23 DUP REM L57 L114 L116 L115 (8 DUPLICATES REMOVED)
                  ANSWERS '1-3' FROM FILE MEDLINE
                  ANSWERS '4-10' FROM FILE CAPLUS
                  ANSWERS '11-14' FROM FILE BIOSIS
                  ANSWERS '15-20' FROM FILE TOXCENTER
                  ANSWERS '21-23' FROM FILE WPIDS


=> fil medl capl biosis toxcenter wpids
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=> d iall 1-3; d ibib ab hitrn 4-10; d iall 11-20; d ibib ab 21-23


L117 ANSWER 1 OF 23     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    2001563247     MEDLINE
DOCUMENT NUMBER:     21521209   PubMed ID: 11641246
```

TITLE: N-t-Butyl hydroxylamine is an antioxidant that reverses age-related changes in mitochondria in vivo and in vitro.
AUTHOR: Atamna H; Robinson C; Ingersoll R; Elliott H; Ames B N
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley/CHORI, Oakland, California 94609, USA.
CONTRACT NUMBER: AG17140 (NIA)
ES01896 (NIEHS)
SOURCE: FASEB JOURNAL, (2001 Oct) 15 (12) 2196-204.
Journal code: 8804484. ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011022
Last Updated on STN: 20020122
Entered Medline: 20011204

applicant's different IE

ABSTRACT:
N-t-butyl hydroxylamine (NtBHA) delays senescence-dependent changes in human lung fibroblasts (IMR90) (Atamna et al., J. Biol. Chem. 275, 6741-6748). The current study examines the effect of NtBHA on mitochondria in old and young rats and human primary fibroblasts (IMR90). In NtBHA-treated rats, the age-dependent decline in food consumption and ambulatory activity was reversed without affecting body weight. The respiratory control ratio of mitochondria from liver of old rats improved after feeding NtBHA. These findings suggest that NtBHA improved mitochondrial function in vivo. The age-dependent increase in proteins with thiol-mixed disulfides was significantly lower in old rats treated with NtBHA. NtBHA was effective only in old rats; no significant effect was observed in young rats. In IMR90 cells, NtBHA delayed senescence-associated changes in mitochondria and cellular senescence induced by maintaining the cells under suboptimal levels of growth factors. Proteasomal activity was also higher in cells treated with NtBHA than in untreated cells. NtBHA accumulates in cells 10- to 15-fold the extracellular concentration and is maintained by mitochondrial NADH. NtBHA is an antioxidant that is recycled by mitochondrial electron transport chain and prevents radical-induced toxicity to mitochondria.

CONTROLLED TERM: Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Aging: DE, drug effects
Antioxidants: ME, metabolism
*Antioxidants: PD, pharmacology
Behavior, Animal
Cell Aging: DE, drug effects
Cell Line
Culture Media
Cysteine Endopeptidases: DE, drug effects
Eating: DE, drug effects
Growth Substances: PH, physiology
Hydroxylamines: ME, metabolism
*Hydroxylamines: PD, pharmacology
Mitochondria: DE, drug effects
Mitochondria: ME, metabolism
*Mitochondria: PH, physiology
Multienzyme Complexes: DE, drug effects
NAD: PH, physiology
Oxidative Stress: DE, drug effects
Rats
Rats, Inbred F344

CAS REGISTRY NO.: **16649-50-6 (N-tert-butylhydroxylamine)**; 53-84-9 (NAD)
CHEMICAL NAME: 0 (Antioxidants); 0 (Culture Media); 0 (Growth Substances); 0 (Hydroxylamines); 0 (Multienzyme Complexes); EC 3.4.22

(Cysteine Endopeptidases); EC 3.4.99.46 (multicatalytic endopeptidase complex)

L117 ANSWER 2 OF 23 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999187978 MEDLINE
DOCUMENT NUMBER: 99187978 PubMed ID: 10087986
TITLE: Two mechanisms for toxic effects of hydroxylamines in human erythrocytes: involvement of free radicals and risk of potentiation.
AUTHOR: Evelo C T; Spooren A A; Bisschops R A; Baars L G; Neis J M
CORPORATE SOURCE: Department of Pharmacology, Universiteit Maastricht, The Netherlands.. c.evelo@farmaco.unimaas.nl
SOURCE: BLOOD CELLS, MOLECULES, AND DISEASES, (1998 Sep) 24 (3) 280-95.
Journal code: 9509932. ISSN: 1079-9796.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990503

ABSTRACT:
The toxic potency of three industrially used hydroxylamines was studied in human blood cells in vitro. The parent compound hydroxylamine and the O-ethyl derivative gave very similar results. Both compounds induced a high degree of methemoglobin formation and glutathione depletion. Cytotoxicity was visible as Heinz body formation and hemolysis. High levels of lipid peroxidation occurred, in this respect O-ethyl hydroxylamine was more active than hydroxylamine. In contrast H2O2 induced lipid peroxidation was lowered after O-ethyl hydroxylamine or hydroxylamine treatment, this is explained by the ferrohemoglobin dependence of H2O2 induced radical species formation. Glutathione S-transferase (GST) and NADPH methemoglobin reductase (NADPH-HbR) activities were also impaired, probably as a result of the radical stress occurring. The riboflavin availability was decreased. Other enzyme activities glutathione reductase (GR), glucose 6-phosphate dehydrogenase (G6PDH), glucose phosphate isomerase and NADH methemoglobin reductase, were not or only slightly impaired by hydroxylamine or O-ethyl hydroxylamine treatment. A different scheme of reactivity was found for N,O-dimethyl hydroxylamine. This compound gave much less methemoglobin formation and no hemolysis or Heinz body formation at concentrations up to and including 7 mM. Lipid peroxidase induction was not detectable, but could be induced by subsequent H2O2 treatment. GST and NADPH-HbR activities and riboflavin availability were not decreased. On the other hand GR and G6PDH activities were inhibited. These results combined with literature data indicate the existence of two different routes of hematotoxicity induced by hydroxylamines. Hydroxylamine as well as O-alkylated derivatives primarily induce methemoglobin, a process involving radical formation. The radical stress occurring is probably responsible for most other effects. N-alkylated species like N,O-dimethyl hydroxylamine primarily lead to inhibition of the protective enzymes G6PDH and GR. Since these enzymes play a key role in the protection of erythrocytes against oxidative stress a risk of potentiation during mixed exposure does exist.

CONTROLLED TERM: Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't
*Dimethylamines: TO, toxicity
Drug Synergism
*Enzyme Inhibitors: PD, pharmacology
Erythrocyte Membrane: DE, drug effects
*Erythrocytes: DE, drug effects
Erythrocytes: EN, enzymology
Erythrocytes: UL, ultrastructure
Free Radicals

Glucosephosphate Dehydrogenase: AI, antagonists & inhibitors
Glutathione: BL, blood
Heinz Bodies
Hemolysis: DE, drug effects
*Hydroxylamines: TO, toxicity
Lipid Peroxidation
Methemoglobin: BI, biosynthesis
Models, Chemical
*Oxidants: PD, pharmacology
Oxidation-Reduction
Oxidative Stress

CAS REGISTRY NO.: 5725-96-2 (N,N-dimethylhydroxylamine); **593-77-1 (N-methylhydroxylamine)**; 67-62-9 (methoxyamine); 70-18-8 (Glutathione); 9008-37-1 (Methemoglobin)

CHEMICAL NAME: 0 (Dimethylamines); 0 (Enzyme Inhibitors); 0 (Free Radicals); 0 (Hydroxylamines); 0 (Oxidants); EC 1.1.1.49 (Glucosephosphate Dehydrogenase)

L117 ANSWER 3 OF 23 MEDLINE
ACCESSION NUMBER: 2001258252 MEDLINE
DOCUMENT NUMBER: 21105781 PubMed ID: 11166356
TITLE: On the anti-aging activities of aminoguanidine and N-t-butylhydroxylamine.
AUTHOR: Hipkiss A R
CORPORATE SOURCE: Division of Biomolecular Sciences, GKT School of Biomedical Sciences, King's College London, Guy's Campus, London Bridge, SE1 1UL, London, UK.. alan.hipkiss@kcl.ac.uk
SOURCE: MECHANISMS OF AGEING AND DEVELOPMENT, (2001 Feb) 122 (2) 169-71.
Journal code: 0347227. ISSN: 0047-6374.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517
CONTROLLED TERM: Check Tags: Human
Antioxidants: PD, pharmacology
Carnosine: PD, pharmacology
***Cell Aging: DE, drug effects**
Cells, Cultured
Glycosylation
*Guanidines: PD, pharmacology
*Hydroxylamines: PD, pharmacology
Proteins: CH, chemistry
Proteins: ME, metabolism
CAS REGISTRY NO.: **16649-50-6 (N-tert-butylhydroxylamine)**; 305-84-0 (Carnosine); 79-17-4 (pimagedine)
CHEMICAL NAME: 0 (Antioxidants); 0 (Guanidines); 0 (Hydroxylamines); 0 (Proteins)

L117 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
ACCESSION NUMBER: 2000:745453 CAPLUS
DOCUMENT NUMBER: 134:96381
TITLE: A Study on the Interaction between Hydroxylamine Analogues and Oxyhemoglobin in Intact Erythrocytes
AUTHOR(S): Spooren, Anita A. M. G.; Evelo, Chris T. A.; Jaffe,

Searched by Barb O'Bryen, STIC 308-4291

Ernst
CORPORATE SOURCE: Department of Pharmacology, Toxicology Section, Universiteit Maastricht, Maastricht, 6200 MD, Neth.
SOURCE: Blood Cells, Molecules & Diseases (2000), 26(4), 373-386
CODEN: BCMDFX; ISSN: 1079-9796
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The oxidative potency of hydroxylamine (HYAM) and its O-derivs. (O-methyl- and O-Et hydroxylamine) is generally larger than the effects of the N-derivs. (N-methyl-, N-dimethyl-, and N,O-di-Me hydroxylamine). The effects of the two groups of hydroxylamines also differ in a qual. sense. To elucidate this difference in toxicity profiles we investigated the Hb dependence of the toxicity, the occurrence of cell-damaging products like superoxide and H2O2, and the cellular kinetics of the hydroxylamine analogs. All hydroxylamines were found to depend on the presence and accessibility of oxyHb to exert their toxicity. This did not provide an explanation for the different toxicity profiles. The interaction of some hydroxylamines with oxyHb is known to lead to the formation of radical intermediates. Differences in the stability of these radical products are known to occur, and in some cases secondary products are formed. This can contribute to the differences in toxicity. In this respect, prodn. of superoxide radicals was demonstrated for all hydroxylamines in the reaction with oxyHb. Evidence for H2O2 generation during the reaction of HYAM, O-Me, O-ethyl-, and N-dimethyl hydroxylamine with oxyHb was also found. Next to variations in the products formed, differences in cellular kinetics are likely to be among the most important factors that explain the different toxicity patterns seen for the hydroxylamines in erythrocytes. Indeed, differences were found to exist for the kinetics of metHb formation in erythrocytes. Not only was the final level of metHb formed much lower for the N-derivs., but also the reaction rate with oxyHb was slower than with HYAM and its O-derivs. Except for N,O-di-Me hydroxylamine (NODMH), the same pattern was seen in hemolyzates. NODMH tripled its effect on Hb in hemolyzate compared with incubations in erythrocytes. This implies that cellular uptake is a limiting factor for NODMH. Since formation of H2O2 is most likely a result of an interaction with Hb, differences in kinetics of metHb formation can be an explanation for the fact that NMH and NODMH did not produce H2O2 to a detectable level. These results indicate that (a) the toxicity of all hydroxylamines depends on an interaction with oxyHb; (b) the interaction with Hb produces radical intermediates and concomitantly superoxide radicals and H2O2; and (c) differences in uptake, reaction rate with Hb, and stability of the intermediates formed do exist for the different hydroxylamines and contribute to their differences in toxicity. (c) 2000 The Blood Cells Foundation, La Jolla, CA, USA.

IT **593-77-1**, N-Methyl hydroxylamine
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interaction between hydroxylamine analogs and oxyHb in intact erythrocytes)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L117 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
ACCESSION NUMBER: 1998:479037 CAPLUS
DOCUMENT NUMBER: 129:117867
TITLE: 2,4-disulfophenylbutyl nitrone, preparation thereof, its salts, and their use as pharmaceuticals for treatment of nervous system oxidn. or antitumor agent caused **oxidative damage**
INVENTOR(S): Carney, John M.

Searched by Barb O'Bryen, STIC 308-4291

PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; University of Kentucky Research Foundation
SOURCE: U.S., 16 pp., Cont.-in-part of U.S. 5,488,145.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5780510	A	19980714	US 1997-663316	19970619
US 5488145	A	19960130	US 1993-173579	19931223
IL 112129	A1	19991231	IL 1994-112129	19940922
WO 9517876	A2	19950706	WO 1994-US14545	19941222
WO 9517876	A3	19950810		
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2001010953	A2	20010116	JP 2000-150128	19941222
US 5508305	A	19960416	US 1995-468564	19950606

PRIORITY APPLN. INFO.: US 1993-173579 A2 19931223
WO 1994-US14545 W 19941222
IL 1994-111037 A3 19940922
JP 1995-518098 A3 19941222
US 1995-426961 A3 19950424

AB 2,4-Disulfonyl .alpha.-phenyl-tert-Bu nitrone and its pharmaceutically acceptable salts are disclosed. These materials are useful as pharmaceutical agents for oral or parenteral, e.g. i.v. administration to patients suffering from acute central nervous system oxidn. as occurs in a stroke or from gradual central nervous system oxidn. which can exhibit itself as progressive central nervous system function loss. The materials are also used to ameliorate the side effects of oxidative-damage-causing antineoplastic disease treatments. The compds. of the invention are useful radical-trapping agents.

IT **16649-50-6P**, N-t-Butylhydroxylamine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction; disulfophenylbutyl nitrone, prepn., salts, and use as pharmaceuticals for treatment of nervous system oxidn. or antitumor agent-caused **oxidative damage**)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L117 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 6
ACCESSION NUMBER: 1995:806481 CAPLUS
DOCUMENT NUMBER: 123:188635
TITLE: 2,4-Disulfonyl phenyl tert-butyl nitrone, its preparation, its salts, and their use as pharmaceuticals for treatment of CNS oxidn. or side effects of **oxidative-damage**-causing antineoplastic disease treatments
INVENTOR(S): Carney, John M.
PATENT ASSIGNEE(S): Oklahoma Medical Research Foundation, USA; University of Kentucky Research Foundation
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9517876	A2	19950706	WO 1994-US14545	19941222
WO 9517876	A3	19950810		
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5488145	A	19960130	US 1993-173579	19931223
IL 112129	A1	19991231	IL 1994-112129	19940922
CA 2179521	AA	19950706	CA 1994-2179521	19941222
CA 2179521	C	20020319		
AU 9515527	A1	19950717	AU 1995-15527	19941222
AU 679835	B2	19970710		
EP 736004	A1	19961009	EP 1995-907224	19941222
EP 736004	B1	20000510		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09507232	T2	19970722	JP 1994-518098	19941222
CN 1156447	A	19970806	CN 1994-194993	19941222
CN 1070176	B	20010829		
BR 9408378	A	19970819	BR 1994-8378	19941222
HU 76788	A2	19971128	HU 1996-1739	19941222
AT 192736	E	20000515	AT 1995-907224	19941222
ES 2145264	T3	20000701	ES 1995-907224	19941222
RU 2159231	C2	20001120	RU 1996-115200	19941222
JP 2001010953	A2	20010116	JP 2000-150128	19941222
SK 282403	B6	20020107	SK 1996-788	19941222
CZ 289629	B6	20020313	CZ 1996-1775	19941222
PL 185189	B1	20030331	PL 1994-315154	19941222
US 5475032	A	19951212	US 1995-426961	19950424
US 5508305	A	19960416	US 1995-468564	19950606
NO 9602637	A	19960813	NO 1996-2637	19960620
FI 9602589	A	19960820	FI 1996-2589	19960620
US 5780510	A	19980714	US 1997-663316	19970619
HK 1001768	A1	20011228	HK 1998-100831	19980204
HK 1008294	A1	20001215	HK 1998-109078	19980711

PRIORITY APPLN. INFO.:			
US 1993-173579	A	19931223	
IL 1994-111037	A3	19940922	
JP 1995-518098	A3	19941222	
WO 1994-US14545	W	19941222	
US 1995-426961	A3	19950424	

AB 2,4-Disulfonyl .alpha.-phenyl-tert-Bu nitrone (I) and its pharmaceutically acceptable salts are disclosed. These materials are useful as pharmaceutical agents for oral or parenteral, e.g. i.v., administration to patients suffering from acute central nervous system oxidn. as occurs in a stroke or from gradual central nervous system oxidn. which can exhibit itself as progressive central nervous system function loss. The materials are also used to ameliorate the side effects of oxidative-damage-causing antineoplastic disease treatments. Prepn. of I is described, is the ability of I e.g. to protect against neuron loss following brain ischemia and reperfusion injury and to protect against the loss of temporal/spatial short-term memory following ischemia.

IT **16649-50-6P**, N-t-Butylhydroxylamine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(disulfonyl Ph t-Bu nitrone, its salts, and their use for treatment of CNS oxidn. or side effects of **oxidative-damage**-causing antineoplastic disease treatments)

L117 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:411990 CAPLUS
DOCUMENT NUMBER: 137:244983
TITLE: Reaction of carnosine with aged proteins: Another

protective process?
AUTHOR(S): Hipkiss, Alan R.; Brownson, Carol; Bertani, Mariana F.; Ruiz, Emilio; Ferro, Albert
CORPORATE SOURCE: GKT School of Biomedical Sciences, King's College London, London, SE1 1UL, UK
SOURCE: Annals of the New York Academy of Sciences (2002), 959(Increasing Health Life Span), 285-294
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Cellular aging is often assocd. with an increase in protein carbonyl groups arising from oxidn.- and glycation-related phenomena and suppressed proteasome activity. These "aged" polypeptides may either be degraded by 20S proteasomes or cross-link to form structures intractable to proteolysis and inhibitory to proteasome activity. Carnosine (.beta.-alanyl-L-histidine) is present at surprisingly high levels (up to 20 mM) in muscle and nervous tissues in many animals, esp. long-lived species. Carnosine can delay senescence in cultured human fibroblasts and reverse the senescent phenotype, restoring a more juvenile appearance. As better antioxidants/free-radical scavengers than carnosine do not demonstrate these antisenescent effects, addnl. properties of carnosine must contribute to its antisenescent activity. Having shown that carnosine can react with protein carbonyls, thereby generating "carnosinylated" polypeptides using model systems, we propose that similar adducts are generated in senescent cells exposed to carnosine. Polypeptide-carnosine adducts have been recently detected in beef products that are relatively rich in carnosine, and carnosine's reaction with carbonyl functions generated during amino acid deamidation has also been described. Growth of cultured human fibroblasts with carnosine stimulated proteolysis of long-labeled proteins as the cells approached their "Hayflick limit," consistent with the idea that carnosine ameliorates the senescence-assocd. proteolytic decline. We also find that carnosine suppresses induction of heme-oxygenase-1 activity following exposure of human endothelial cells to a glycated protein. The antisenescent activity of the spin-trap agent .alpha.-phenyl-N-t-butylnitrone (PBN) towards cultured human fibroblasts resides in N-t-butyl-hydroxylamine, its hydrolysis product. As hydroxylamines are reactive towards aldehydes and ketones, the antisenescent activity of N-t-butyl-hydroxylamine and other hydroxylamines may be mediated, at least in part, by reactivity towards macromol. carbonyls, analogous to that proposed for carnosine.
IT **16649-50-6**, N-tert-Butyl-hydroxylamine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reaction of carnosine with aged protein carbonyls and its antisenescence effect in cultured human fibroblasts in comparison with antisenescent activity of N-t-butyl-hydroxylamine)
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L117 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:380392 CAPLUS
DOCUMENT NUMBER: 134:361362
TITLE: Aryl nitrone therapeutics and methods for treating inflammatory bowel disease
INVENTOR(S): Flitter, William D.; Garland, William A.
PATENT ASSIGNEE(S): Centaur Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035951	A2	20010525	WO 2000-US31018	20001113
WO 2001035951	A3	20020110		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6545056	B1	20030408	US 2000-716023	20001117

PRIORITY APPLN. INFO.: US 1999-166243P P 19991118

AB Disclosed are methods for treating or preventing inflammatory bowel disease (IBD) using aryl nitrone compds. Pharmaceutical compns. contg. aryl nitrone compds. which are useful for the treatment or prophylaxis of IBD are also disclosed. Several nitrones such as .alpha.-(3-ethoxy-4-methoxyphenyl)-N-cyclohexylnitrone were tested and shown effective in animal models of inflammatory bowel disease.

IT **16649-50-6P**, N-t-Butylhydroxylamine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(aryl nitrone therapeutics and methods for treating inflammatory bowel disease)

L117 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:770674 CAPLUS
DOCUMENT NUMBER: 136:51467
TITLE: On the "struggle between chemistry and biology during aging" - implications for DNA repair, apoptosis and proteolysis, and a novel route of intervention
AUTHOR(S): Hipkiss, Alan R.
CORPORATE SOURCE: Division of Biomolecular Sciences, King's College London, London, SE1 1UL, UK
SOURCE: Biogerontology (2001), 2(3), 173-178
CODEN: BIOGCN; ISSN: 1389-5729
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The possible effects of specific spontaneous changes in protein chem. on age-related homeostatic dysfunction are discussed. Spontaneous racemization and isomerization of aspartic acid and deamidation of asparagine to four possible forms of aspartic acid in caspases and their substrates could profoundly alter apoptotic activity. Deamidation of asparagine residues at critically important sites of DNA glycosylases could compromise base excision repair activity. Furthermore, as oxidative damage may enhance asparagine/aspartate instability in proteins, and erroneously-synthesized proteins show increased susceptibility to oxidative attack, it is beginning to appear that the aberrant protein forms that accumulate during aging are possibly interrelated. The role of cell growth rates in controlling constitutive proteolytic elimination of various forms of aberrant polypeptides is then discussed. Finally, it is pointed out that three recently described agents that delay senescence in cultured cells (aminoguanidine, N-t-butylhydroxylamine and kinetin) resemble carnosine in that they are also likely to react with glycoxidized proteins, as well as possess anti-oxidant activity. These observations suggest that pluripotency may be a necessary pre-requisite for effective anti-aging activity.

IT **16649-50-6**, N-t-Butylhydroxylamine
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(anti-aging agents and DNA repair, apoptosis and proteolysis in aging)
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L117 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:20589 CAPLUS
DOCUMENT NUMBER: 116:20589
TITLE: Proton and carbon-13 NMR spectra of (Z)-C-aryl N-tert-butyl nitrones
AUTHOR(S): Murray, Robert W.; Singh, Megh
CORPORATE SOURCE: Dep. Chem., Univ. Missouri, St. Louis, MO, USA
SOURCE: Magnetic Resonance in Chemistry (1991), 29(9), 962-3
CODEN: MRCHEG; ISSN: 0749-1581
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 116:20589
AB The 1H and 13C NMR spectra of 12 (Z)-C-aryl N-tert-Bu nitrones were measured and proton and carbon assignments made. The nitrones were synthesized by the dimethyldioxirane method.
IT **16649-50-6**, tert-Butylhydroxylamine
RL: PROC (Process)
(conversion of, to aryl tert-Bu nitrones)

L117 ANSWER 11 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. DUPLICATE 2
ACCESSION NUMBER: 2000:314634 BIOSIS
DOCUMENT NUMBER: PREV200000314634
TITLE: N-t-butyl hydroxylamine, a hydrolysis product of alpha-phenyl-N-t-butyl nitrone, is more potent in delaying senescence in human lung fibroblasts.
AUTHOR(S): Atamna, Hani; Paler-Martinez, Andres; Ames, Bruce N. (1)
CORPORATE SOURCE: (1) Division of Biochemistry and Molecular Biology, CHORI 5700 Martin Luther King Jr. Way, Oakland, CA, 94609 USA
SOURCE: Journal of Biological Chemistry, (March 10, 2000) Vol. 275, No. 10, pp. 6741-6748. print.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
alpha-Phenyl-N-t-butyl nitrone (PBN), a spin trap, scavenges hydroxyl radicals, protects tissues from oxidative injury, and delays senescence of both normal human lung fibroblasts (IMR90) and senescence-accelerated mice. N-t-butyl hydroxylamine and benzaldehyde are the breakdown products of PBN. N-t-Butyl hydroxylamine delays **senescence** of IMR90 **cells** at concentrations as low as 10 muM compared with 200 muM PBN to produce a similar effect, suggesting that N-t-butyl hydroxylamine is the active form of PBN. N-Benzyl hydroxylamine and N-methyl hydroxylamine compounds unrelated to PBN were also effective in delaying senescence, suggesting the active functional group is the N-hydroxylamine. All the N-hydroxylamines tested significantly decreased the endogenous production of oxidants, as measured by the oxidation of 2',7'-dichlorodihydrofluorescin and the increase in the GSH/GSSG ratio. The acceleration of senescence induced by hydrogen peroxide is reversed by the N-hydroxylamines. DNA damage, as determined by the level of apurinic/apyrimidinic sites, also decreased significantly following treatment with N-hydroxylamines. The N-hydroxylamines appear to be effective through mitochondria; they delay age-dependent changes in mitochondria as measured by accumulation of rhodamine-123, they prevent reduction of cytochrome CFeIII by superoxide radical, and they reverse an age-dependent decay of mitochondrial aconitase, suggesting they react with the superoxide radical.

applicants but different IE

CONCEPT CODE: Respiratory System - General; Methods *16001
Genetics and Cytogenetics - General *03502
Comparative Biochemistry, General *10010
Biochemical Methods - General *10050
Biochemical Methods - Nucleic Acids, Purines and Pyrimidines *10052
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - General *10060
Biophysics - General Biophysical Studies *10502
Tissue Culture, Apparatus, Methods and Media *32500
Toxicology - General; Methods and Experimental *22501
In Vitro Studies, Cellular and Subcellular *32600
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Physiology, General and Miscellaneous - General *12002
Pathology, General and Miscellaneous - General *12502
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Energy and Respiratory Metabolism *13003

BIOSYSTEMATIC CODE: Hominidae 86215
Muridae 86375

INDEX TERMS: Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Methods and Techniques; Respiratory System (Respiration)

INDEX TERMS: Parts, Structures, & Systems of Organisms
lung: respiratory system; lung fibroblasts: analysis, respiratory system, senescence delay; mitochondria; mitochondrial membranes

INDEX TERMS: Chemicals & Biochemicals
DNA: analysis, damage; N-t-butyl hydroxylamine: analysis, functions; alpha-phenyl-N-t-butyl nitrone: analysis, functions; cytochromes: analysis; enzymes: analysis; mitochondrial enzymes: analysis, functions; superoxide radical: analysis

INDEX TERMS: Methods & Equipment
enzyme activity assays: activity assays, analytical method; tissue culture: Cell Culture Techniques, culture method

ORGANISM: Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGANISM: Organism Name
human (Hominidae); mouse (Muridae)

ORGANISM: Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates

REGISTRY NUMBER: **16649-50-6** (N-T-BUTYL HYDROXYLAMINE)

L117 ANSWER 12 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:420142 BIOSIS
DOCUMENT NUMBER: PREV200200420142
TITLE: Delaying brain mitochondrial decay and aging with mitochondrial **antioxidants** and metabolites.
AUTHOR(S): Liu, Jiankang; Atamna, Hani; Kuratsune, Hirohiko; Ames, Bruce N. (1)
CORPORATE SOURCE: (1) Children's Hospital Oakland Research Institute, 5700 Martin Luther King Jr. Way, Oakland, CA, 94609: bnames@uclink4.berkeley.edu USA
SOURCE: Harman, Denham [Editor]. Annals of the New York Academy of Sciences, (April, 2002) Vol. 959, pp. 133-166. Annals of the New York Academy of Sciences. Increasing healthy life span: Conventional measures and slowing the innate aging

process. print.
Publisher: New York Academy of Sciences 2 East 63rd Street, New York, NY, 10021, USA.
Meeting Info.: Ninth Congress of the International Association of Biomedical Gerontology (IABG) on Increasing Healthy Life Span: Conventional Measures and Slowing the Innate Aging Process Vancouver, BC, Canada June 27-30, 2001 International Association of Biomedical Gerontology
. ISSN: 0077-8923. ISBN: 1-57331-360-2 (cloth), 1-57331-361-0 (paper).
DOCUMENT TYPE: Book; Conference
LANGUAGE: English
CONCEPT CODE: General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Lipids *10066
Metabolism - General Metabolism; Metabolic Pathways *13002
Nervous System - Physiology and Biochemistry *20504
Gerontology *24500
Pediatrics *25000
BIOSYSTEMATIC CODE: Hominidae 86215
Muridae 86375
INDEX TERMS: Major Concepts
Aging; Metabolism; Nervous System (Neural Coordination)
INDEX TERMS: Parts, Structures, & Systems of Organisms
brain: aging, mitochondrial decay, nervous system; fibroblast cells: diploid
INDEX TERMS: Chemicals & Biochemicals
DNA; N-t-butyl hydroxylamine: **antioxidant**; RNA; alpha-phenyl-N-t-butyl nitrone: **antioxidant**; carnitine acetyltransferase; lipid; protein
INDEX TERMS: Miscellaneous Descriptors
Book Chapter; Meeting Paper
ORGANISM: Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGANISM: Organism Name
human (Hominidae); mouse (Muridae); rat (Muridae): old, young
ORGANISM: Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates
REGISTRY NUMBER: **16649-50-6** (N-T-BUTYL HYDROXYLAMINE)
9029-90-7 (CARNITINE ACETYLTRANSFERASE)

L117 ANSWER 13 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:167037 BIOSIS
DOCUMENT NUMBER: PREV200300167037
TITLE: **Oxidative stress** and **cellular aging** increase metal content in cultured human fibroblasts, which can be attenuated by hydroxylamines.
AUTHOR(S): Killilea, D. W. (1); Atamna, H. (1); Ames, B. N. (1)
CORPORATE SOURCE: (1) Children's Hospital Oakland Research Institute, Oakland, CA, USA USA
SOURCE: Molecular Biology of the Cell, (Nov., 2002, 2002) Vol. 13, No. Supplement, pp. 392a-393a. print.
Meeting Info.: 42nd Annual Meeting of the American Society

for Cell Biology San Francisco, CA, USA December 14-18, 2002 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English
CONCEPT CODE: General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Cytology and Cytochemistry - General *02502
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Minerals *10069
Metabolism - General Metabolism; Metabolic Pathways *13002
Gerontology *24500
BIOSYSTEMATIC CODE: Hominidae 86215
INDEX TERMS: Major Concepts
Aging; Cell Biology; Metabolism
INDEX TERMS: Chemicals & Biochemicals
N-tert-butylhydroxylamine: **cellular aging**
attenuation, **cellular** metal content increase
attenuation; iron: aging-induced fibroblast increase, **oxidative stress**-induced fibroblast
increase; magnesium: aging-induced fibroblast increase, **oxidative stress**-induced fibroblast
increase; manganese: aging-induced fibroblast increase, **oxidative stress**-induced fibroblast
increase; zinc: aging-induced fibroblast increase, **oxidative stress**-induced fibroblast
increase
INDEX TERMS: Miscellaneous Descriptors
Meeting Abstract
ORGANISM: Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISM: Organism Name
IMR-90s **cell** line (Hominidae): **aging**
-related changes, human fibroblast cell line, **oxidative stress**
ORGANISM: Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
REGISTRY NUMBER: **16649-50-6** (N-TERT-BUTYLHYDROXYLAMINE)
7439-89-6 (IRON)
7439-95-4 (MAGNESIUM)
7439-96-5 (MANGANESE)
7440-66-6 (ZINC)

L117 ANSWER 14 OF 23 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:24976 BIOSIS
DOCUMENT NUMBER: PREV200300024976
TITLE: Loss of metal homeostasis associated with **cellular aging** is delayed by N-t-butyl-hydroxylamine.
AUTHOR(S): Killilea, David W. (1); Atamna, Hani (1); Ames, Bruce N. (1)
CORPORATE SOURCE: (1) Children's Hospital Oakland Research Institute, Oakland, CA, USA USA
SOURCE: Free Radical Biology & Medicine, (2002) Vol. 33, No. Supplement 2, pp. S314. print.
Meeting Info.: 9th Annual Meeting of the Oxygen Society San Antonio, Texas, USA November 20, 2002 International Society for Free Radical Research
. ISSN: 0891-5849.
DOCUMENT TYPE: Conference
LANGUAGE: English
CONCEPT CODE: General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520

Cytology and Cytochemistry - General *02502
Cytology and Cytochemistry - Animal *02506
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General *10060
Biochemical Studies - Minerals *10069
BIOSYSTEMATIC CODE: Hominidae 86215
INDEX TERMS: Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology
INDEX TERMS: Parts, Structures, & Systems of Organisms
fibroblast
INDEX TERMS: Chemicals & Biochemicals
N-t-butyl-hydroxylamine; hydrogen peroxide; iron; magnesium; manganese; zinc
INDEX TERMS: Miscellaneous Descriptors
cellular aging; oxidative stress; Meeting Abstract
ORGANISM: Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISM: Organism Name
IMR-90 cell line (Hominidae)
ORGANISM: Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
REGISTRY NUMBER: **16649-50-6** (N-T-BUTYL-HYDROXYLAMINE)
7722-84-1 (HYDROGEN PEROXIDE)
7439-89-6 (IRON)
7439-95-4 (MAGNESIUM)
7439-96-5 (MANGANESE)
7440-66-6 (ZINC)

L117 ANSWER 15 OF 23 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:127588 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA13708108676M
TITLE: Delaying brain mitochondrial decay and aging with mitochondrial **antioxidants** and metabolites
AUTHOR(S): Liu, Jiankang; Atamna, Hani; Kuratsune, Hirohiko; Ames, Bruce N.
CORPORATE SOURCE: Division of Biochemistry and Molecular Biology, University of California, Berkeley, CA, 94720, USA.
SOURCE: Annals of the New York Academy of Sciences, (2002) Vol. 959, No. Increasing Health Life Span, pp. 133-166.
CODEN: ANYAA9. ISSN: 0077-8923.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2002:411980
LANGUAGE: English
ENTRY DATE: Entered STN: 20020605
Last Updated on STN: 20020820

ABSTRACT:
A review. Mitochondria decay with age due to oxidn. changes of lipids, proteins, RNA, and DNA. Some of this decay can be reversed in aged animals by feeding the mitochondrial metabolites acetylcarnitine and .alpha.-lipoic acid. Recent data on the effects of these mitochondrial metabolites and mitochondrial ***antioxidants*** (.alpha.-phenyl-N-tert-Bu nitrone, N-tert-Bu hydroxylamine) on the age-assocd. mitochondrial decay in the brain of old rats, neuronal cells, and human diploid fibroblast cells are summarized. In the feeding studies with old rats, the mitochondrial metabolites and ***antioxidants*** improved the age-assocd. decline of ambulatory activity and memory, partially restored mitochondrial structure and functions, inhibited the age-assocd. increases of **oxidative damage** to lipids, proteins and nucleic acids, elevated the levels of **antioxidants**, and

restored the activity and substrate binding affinity of the key mitochondrial enzyme, carnitine acetyltrasferase. The mitochondrial metabolites and ***antioxidants*** **protected** the neuronal **cells** from neurotoxin- and oxidant-induced toxicity and **oxidative damage**, delayed the normal senescence of human diploid fibroblast cells, and inhibited the oxidant-induced acceleration of senescence. The results suggest a plausible mechanism: with age, increased **oxidative damage** to proteins and lipid membranes, particularly in mitochondria, causes deformations of the enzyme structures, with consequent decreases of enzyme activities and substrate binding affinities for their substrates. Increased levels of substrates restore the reaction rates and mitochondrial functions, thus delaying mitochondrial decay and aging. This loss of activity due to coenzyme or substrate binding appears to be true for a no. of other enzymes as well, including mitochondrial complex III and IV.
CLASSIFICATION CODE: 18-0
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
review nutrition **antioxidant** brain mitochondria membrane damage aging
REGISTRY NUMBER: 1200-22-2 (.alpha.-Lipoic acid)
3040-38-8 (Acetylcarnitine)
3376-24-7 (.alpha.-Phenyl-N-tert-butyl nitrone)
16649-50-6 (N-Tert-Butyl hydroxylamine)

L117 ANSWER 16 OF 23 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:188095 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA136070959377
TITLE: N-tert-Butyl hydroxylamine is an **antioxidant** that reverses age-related changes in mitochondria in vivo and in vitro
CORPORATE SOURCE: Department of Molecular and Cell Biology, Univ. of California, Berkeley, CA, 94609, USA.
SOURCE: FASEB Journal, (2001) Vol. 15, No. 12, pp. 2196-2204.
CODEN: FAJOEC. ISSN: 0892-6638.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2001:749542
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020212

ABSTRACT:
This study examd. the effect of N-tert-Bu hydroxylammine (NtBHA) on liver mitochondria in old and young rats and on human primary fibroblasts (IMR90). In NtBHA-treated rats, the age-dependent decline in food consumption and ambulatory activity was reversed without affecting body wt. The respiratory control ratio of mitochondria from the liver of old rats improved after feeding NtBHA. These findings suggest that NtBHA improved mitochondrial function in vivo. The age-dependent increase in proteins with thiol-mixed disulfides was lower in old rats treated with NtBHA than in controls.. NtBHA was effective only in old rats; no significant effect was obsd. in young rats. In IMR90 ***cells*** , NtBHA delayed senescence-assocd. changes in mitochondria and **cellular senescence** induced by maintaining the cells under suboptimal levels of growth factors. Proteasomal activity was also higher in cells treated with NtBHA than in untreated cells. NtBHA accumulated in cells to 10-15-fold the extracellular concn. and was maintained by mitochondrial NADH. NtBHA is an **antioxidant** that is recycled by the mitochondrial electron transport chain and prevents radical-induced toxicity to mitochondria.
CLASSIFICATION CODE: 1-11
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
butyl hydroxylamine **antioxidant** mitochondria aging

REGISTRY NUMBER: **16649-50-6** (N-tert-Butyl hydroxylamine)
140879-24-9 (Proteasome)

L117 ANSWER 17 OF 23 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:119889 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA13022292543V
TITLE: Only the glutathione dependent **antioxidant** enzymes are inhibited by hematotoxic hydroxylamines
AUTHOR(S): Spooren, Anita A. M. G.; Evelo, Chris T. A.
CORPORATE SOURCE: Department of Pharmacology, Toxicology Section, Universiteit Maastricht, Maastricht, 6200 MD, Neth..
SOURCE: Human & Experimental Toxicology, (1998) Vol. 17, No. 10, pp. 554-559.
CODEN: HETOEA. ISSN: 0960-3271.
COUNTRY: NETHERLANDS
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1999:122007
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020509

ABSTRACT:
Hydroxylamine and some of its derivs. are known to cause oxidative effects both in vitro and in vivo. In the current study we investigated the effects of hydroxylamines on the enzymic **antioxidant** defense system in human erythrocytes. The activity of catalase and superoxide dismutase was not significantly influenced by any of the hydroxylamines tested. However, the activity of glutathione peroxidase (GPX) and glutathione S-transferase (GST) was strongly inhibited by hydroxylamine and its O-derivs. (O-Me and O-Et hydroxylamine). GPX was also inhibited by two N-derivs. of hydroxylamine (i.e. N-dimethyl and N,O-di-Me hydroxylamine). This indicates that exposure to hydroxylamines not only changes the cellular oxidn.-redn. status but also leads to inhibition of the glutathione dependent **antioxidant** enzymes. GST as well as GPX have cysteine residues at the active site of the enzymes. Such an accessible thiol group is generally susceptible to formation of protein-mixed disulfides or intramol. disulfides. If these thiol groups are essential for activity this would be accompanied by an increase or decrease in the enzyme activity. In principle this is also true for glutathione reductase (GR), which in this study was only inhibited by N,O-di-Me and N-Me hydroxylamines. However, GR is capable to reduce these disulfides by taking up two electrons, either from its substrate NAPDH or from another reductant. Oxidn. of these thiol groups in GR would thus not lead to impairment of GR activity. The fact that NODMH and NMH do decrease the GR activity can therefore only be explained by other modifications. The activity loss of GST and GPX on the other hand, is likely to involve oxidn. of crit. cysteine residues. The practical consequence of these findings is that the cellular prooxidant state that may arise in erythrocytes exposed to hydroxylamines can be further increased by activity loss of protective enzymes, which may decrease the av. life span of the red blood cell.
CLASSIFICATION CODE: 4-3
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
glutathione **antioxidant** enzyme erythrocyte hydroxylamine
REGISTRY NUMBER: 67-62-9 (O-Methyl hydroxylamine)
593-77-1 (N-Methyl hydroxylamine)
624-86-2 (O-Ethyl hydroxylamine)
1117-97-1 (N,O-Dimethyl hydroxylamine)
5725-96-2 (N,N-Dimethyl hydroxylamine)
7803-49-8 (Hydroxylamine)
7803-49-8Q (Hydroxylamine, derivs.)
9001-05-2 (Catalase)
9001-48-3 (Glutathione reductase)

9013-66-5 (Glutathione peroxidase)
9054-89-1 (Superoxide dismutase)
50812-37-8 (Glutathione S-transferase)
70-18-8 (Glutathione)

L117 ANSWER 18 OF 23 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:140570 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA12616207531Q
TITLE: 2,4-Disulfonylphenyl tert-butyl nitrone and its salts as pharmaceutical free radical-trapping agents
AUTHOR(S): Carney, John M.
CORPORATE SOURCE: ASSIGNEE: University of Kentucky Research Foundation
PATENT INFORMATION: ZA 954297 A 24 Jan 1996
SOURCE: (1996) S. African, 48 pp.
CODEN: SFXXAB.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1997:220557
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020626

ABSTRACT:
2,4-Disulfonylphenyl tert-Bu nitrone (I) and its salts have superior efficacy and potency and low toxicity when used in treatment of acute **oxidative** ***damage*** , e.g in the central nervous system as the result of a stroke, or after cancer radiotherapy or chemotherapy. I is also useful in treatment of conditions characterized by protracted low-grade **oxidative** ***stress*** on the central nervous system, e.g. Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multi-infarct dementia, and retinopathy. Thus, 2-methyl-2-nitropropane was reduced with Zn/AcOH to N-(tert-butyl)hydroxylamine, which was condensed with 4-formyl-1,3-benzenedisulfonic acid to form I in 75% yield. Thus, I (50-1000 mg/kg i.p.) completely prevented neuronal loss in gerbils after brain ischemia (bilateral carotid occlusion) and reperfusion.
CLASSIFICATION CODE: 1-11
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
sulfonylphenyl butyl nitrone central nervous disorder;
radical scavenger sulfonylphenyl butyl nitrone;
oxidative stress nervous system nitrone;
cancer chemotherapy radiotherapy nitrone
REGISTRY NUMBER: 88-39-1 (4-Formyl-1,3-benzenedisulfonic acid)
594-70-7 (2-Methyl-2-nitropropane)
16649-50-6 (N-(tert-Butyl)hydroxylamine)
25316-40-9 (Adriamycin)
REGISTRY NUMBER: 168021-77-0; 168021-79-2; 168021-80-5; 168021-81-6; 168021-82-7; 168021-83-8

L117 ANSWER 19 OF 23 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:149728 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA10920180314F
TITLE: Storage-stable silver halide color photographic developing solutions
AUTHOR(S): Ishikawa, Masao; Koboshi, Shigeharu; Kadota, Shinji; Matsushima, Yoko
CORPORATE SOURCE: ASSIGNEE: Konica Co., Ltd.
PATENT INFORMATION: JP 8848549 A2 1 Mar 1988
SOURCE: (1988) Jpn. Kokai Tokkyo Koho, 19.
CODEN: JKXXAF.
COUNTRY: JAPAN
DOCUMENT TYPE: Patent

FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1988:580314
LANGUAGE: Japanese
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20021029

ABSTRACT:
The title solns. contain **antioxidants** R1R2NCX1X2(CX3H)mSO3M (R1-2 = H, alkyl, acyl, carbamoyl; R1-2 may jointly form a ring; X1-3 = H, alkyl; M = H, alkali metal; m = 0-2). The above **antioxidants** are effective in stabilizing developing baths and bear no hazard as compared to conventional products, e.g., hydroxylamine. Thus, 1 L of developing soln. (KOH-adjusted pH 10.10) contg. 3.0 .times. 10-3 mol K2SO3 and KCl 0.3, K2CO3 25.0, H2NCH2SO3H (I) 5.0, polyphosphoric acid 2.0, developer (II) 5.0, and fluorescent brightener 2.0 g, enough water and trace amts. of metal salts showed no change after 10 days in open jar, whereas tar formation was obsd. without the I, or browning with hydroxyurea in place of the I.
CLASSIFICATION CODE: 74-2
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
developing color photog amine stabilizer; sulfone **antioxidant** color photog developing; nontoxic **antioxidant** color photog developing; storage stable **antioxidant** photog developing
REGISTRY NUMBER: 7297-06-5 (2-Amino-1-propanesulfonic acid)
13881-91-9 (Aminomethanesulfonic acid)
23592-45-2 (Methylaminomethanesulfonic acid)
593-77-1 (Methylhydroxylamine)
5725-96-2 (Dimethylhydroxylamine)
REGISTRY NUMBER: 25646-71-3; 50928-80-8; 99893-17-1; 116963-82-7; 107-35-7; 68507-34-6; 116963-83-8; 624-81-7

L117 ANSWER 20 OF 23 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:47837 TOXCENTER
DOCUMENT NUMBER: 88334895 PubMed ID: 2901694
TITLE: Cyclic GMP and cell death in rat cerebellar slices
AUTHOR(S): Garthwaite G; Garthwaite J
CORPORATE SOURCE: Department of Veterinary Physiology and Pharmacology, University of Liverpool, U.K
SOURCE: NEUROSCIENCE, (1988 Jul) 26 (1) 321-6.
Journal Code: 7605074. ISSN: 0306-4522.
COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 88334895
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

ABSTRACT:
Incubated slices of young rat cerebellum were used to examine the possible relationship between the neurotoxic effects of excitatory amino acids and their ability to elicit large increases in the levels of cyclic GMP in this tissue. No cell death was detectable following exposure of the slices to the guanylate cyclase activator, nitroprusside (up to 0.3 mM), the phosphodiesterase inhibitor, isobutylmethylxanthine (0.5 mM), or to cyclic GMP (10 mM) and its dibutyryl and 8-bromo derivatives (0.5 mM). However, incubation of the slices with tbe guanylate cyclase inhibitors, N-methylhydroxylamine and hydroxylamine (0.1-1 mM), methylene blue (10-100 microM), ethacrynic acid (300 microM) and retinol (1 mM) caused a progressive destruction of the differentiating cells. The damage induced by N-methylhydroxylamine and hydroxylamine was inhibited by nitroprusside, cyclic GMP and isobutylmethylxanthine. It could also be reduced by lowering the partial pressure of oxygen, by oxygen radical scavenging enzymes and by omitting Ca2+ from the medium. Oxygen radical generating enzyme systems mimicked the pattern of toxicity of the guanylate cyclase inhibitors but their effects were not reduced by nitroprusside or omission of Ca2+. The

results indicate that guanylate cyclase/cyclic GMP does not mediate amino acid neurotoxicity but, instead, may be part of a protective mechanism against oxygen free radicals.

CONTROLLED TERM: Check Tags: Animal; In Vitro; Support, Non-U.S. Gov't
Cell Survival: DE, drug effects
Cerebellum: DE, drug effects
*Cerebellum: ME, metabolism
*Cyclic GMP: ME, metabolism
Cyclic GMP: PH, physiology
*Enzyme Inhibitors: TO, toxicity
Ethacrynic Acid: TO, toxicity
Free Radicals: ME, metabolism
*Guanylate Cyclase: ME, metabolism
Guanylate Cyclase: PH, physiology
Hydroxylamines: TO, toxicity
Methylene Blue: TO, toxicity
*Neurotoxins: PD, pharmacology
Nitroprusside: TO, toxicity
Rats

REGISTRY NUMBER: 15078-28-1 (Nitroprusside)
58-54-8 (Ethacrynic Acid)
593-77-1 (N-methylhydroxylamine)
61-73-4 (Methylene Blue)
7665-99-8 (Cyclic GMP)

CHEMICAL NAME: 0 (Enzyme Inhibitors); 0 (Free Radicals); 0 (Hydroxylamines); 0 (Neurotoxins); EC 4.6.1.2 (Guanylate Cyclase)

L117 ANSWER 21 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-146789 [19] WPIDS
CROSS REFERENCE: 1999-539193 [45]
DOC. NO. CPI: C2002-045468
TITLE: New process for preparation of an exochelin useful as iron-binding compound for diagnosing and treating disease e.g. myocardial infarction.
DERWENT CLASS: B03
INVENTOR(S): BUSWELL, R L; GERACI, L S; HUDSPETH, J P; LEVY, S G; STEARNS, J F
PATENT ASSIGNEE(S): (KEYS-N) KEYSTONE BIOMEDICAL INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6335443	B1	20020101	(200219)*		16

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6335443	B1	Div ex	US 1998-134457	19980814
			US 1999-263322	19990305

PRIORITY APPLN. INFO: US 1998-134457 19980814; US 1999-263322 19990305

AB US 6335443 B UPAB: 20020321
NOVELTY - Preparation of an exochelin is new.
DETAILED DESCRIPTION - Preparation of an exochelin involves:
(a) reacting a mixture of an acid of formula CO2H-A-CO2H with

dimethyl pimelate, hydrochloric acid, methanol or di-n-butyl ether to produce a methylated acid;

(b) mixing the methylated acid with thionyl chloride and dimethyl formamide to replace an OH group with chlorine;

(c) adding the product of the step (b) to a suspension of O-**benzyl hydroxylamine** hydrochloride and triethylamine in CH2Cl2 to produce an O-benzylmethyl hydroxamate;

(d) adding a solution of di-tert-butyl dicarbonate in tetrahydrofuran (THF) to a solution of (L)-6-hydroxynorleucine and triethylamine in a THF-water;

(e) separating an aqueous layer and acidifying the aqueous layer to pH 3 with citric acid and extracting that layer with ethyl acetate (EtOAc);

(f) drying and purifying the EtAOc layer to produce (L)-N-Boc-6-hydroxynorleucine;

(g) reacting the hydroxynorleucine with allyl bromide to produce (L)-N-Boc-6-hydroxynorleucine allyl ester;

(h) adding carbon tetrabromide in anhydrous dichloromethane (CH2Cl2) and triphenylphosphine to the allyl ester to provide a viscous oil;

(i) adding the oil to EtOAc/hexane to produce (L)-N-Boc-6-bromonorleucine allyl ester (A);

(j) mixing (A) with the O-benzylmethyl hydroxamate, potassium iodide (KI) and potassium carbonate (K2CO3) in anhydrous acetone to produce an (L)-N6-methyl-N6-(benzyloxy)-N2-Boc-lysine allyl ester (A1);

(k) adding trifluoro acetic acid to (A1) to form a solid intermediate and adding the solid intermediate to (L)-N-(2-(benzyloxy)benzoyl)serine and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline to produce an (L)-N6-methyl-N6-(benzyloxy)-N2-((L)-N-(2-(benzyloxy)benzoyl)serine)-lysine allyl ester (A2);

(l) gradually adding thionyl chloride to a solution of (A2) in anhydrous THF and purifying the resultant liquid to produce an (L)-N6-methyl-N6-(benzyloxy)-N2-((S)-2-(2-benzyloxy)phenyl)-2-oxazoline-4-carbonyl)-lysine allyl ester (A3);

(m) adding morpholine and tetrakis(triphenylphosphine)palladium to (A3) in anhydrous CH2Cl2 to produce an acid;

(n) adding (L)-N2-((S)-3-hydroxybutyryl) alpha -amino-N-(benzyloxy)caprolactam in anhydrous THF to the acid and then adding diethyl azodicarboxylate; and

(o) mixing the resultant material with methanol, 10% Pd/c and H2 followed by co-evaporation of methanol and CH2Cl2.

A = optionally saturated aliphatic hydrocarbon.

ACTIVITY - Cardiant; Cytostatic; Antiarteriosclerotic.

MECHANISM OF ACTION - Iron-binders; Iron-mediated oxidant injury inhibitor.

USE - As iron-binding compound for diagnosing and treating disease e.g. reperfusion injury, arteriosclerosis cataract formation, cancer and other degenerative injuries to living tissue. Also useful for treating acute myocardial infarction and cardiac tissue damage, in organ preservation and vessel occlusion following angioplasty.

ADVANTAGE - The method provides an improved synthetic agent (exochelin), which is effective for rapidly chelating metals as they become available, to counteract myocardial infarction, to treat cancer or other conditions driven by the presence of free metals or protect tissue which may be damaged by the hydroxyl radical and related mechanisms imparting cell death and instructions. The exochelin also blocks or significantly reduces **oxidative damage** to tissue resulting from the iron-mediated catalysis of tissue and free radical reactions mediated by the hydroxyl radical.

Dwg.0/6

L117 ANSWER 22 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-514431 [56] WPIDS
DOC. NO. CPI: C2001-153701

TITLE: Preparation of alpha-(2,4-disulfophenyl)-N-tert-butylnitrone compounds by reacting a benzaldehyde with N-**tertbutylhydroxylamine**, useful for treating e.g. CNS disorders, stroke, **oxidative damage** or concussion.

DERWENT CLASS: B05

INVENTOR(S): BLIXT, J; KRUK, H; LARSSON, U; MCGINLEY, J; POUHOV, S; VAJDA, J; WILCOX, A

PATENT ASSIGNEE(S): (ASTR) ASTRAZENECA AB; (CENT-N) CENTAUR PHARM INC; (BLIX-I) BLIXT J; (KRUK-I) KRUK H; (LARS-I) LARSSON U; (MCGI-I) MCGINLEY J; (POUH-I) POUHOV S; (VAJD-I) VAJDA J; (WILC-I) WILCOX A

COUNTRY COUNT: 95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001051461	A1	20010719	(200156)*	EN	19
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001027204	A	20010724	(200166)		
BR 2001007480	A	20020903	(200264)		
NO 2002003318	A	20020815	(200273)		
EP 1250320	A1	20021023	(200277)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
KR 2002091078	A	20021205	(200324)		
US 2003069442	A1	20030410	(200327)		
CN 1394200	A	20030129	(200334)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001051461	A1	WO 2001-SE8	20010104
AU 2001027204	A	AU 2001-27204	20010104
BR 2001007480	A	BR 2001-7480	20010104
		WO 2001-SE8	20010104
NO 2002003318	A	WO 2001-SE8	20010104
		NO 2002-3318	20020709
EP 1250320	A1	EP 2001-901620	20010104
		WO 2001-SE8	20010104
KR 2002091078	A	KR 2002-708863	20020709
US 2003069442	A1	WO 2001-SE8	20010104
		US 2001-806833	20010405
CN 1394200	A	CN 2001-803583	20010104

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001027204	A	Based on	WO 200151461
BR 2001007480	A	Based on	WO 200151461
EP 1250320	A1	Based on	WO 200151461

PRIORITY APPLN. INFO: SE 2000-56 20000110

AB WO 200151461 A UPAB: 20021031
NOVELTY - A process for the preparation of alpha -(2,4-disulfophenyl)1-N-tert-butylnitrone comprise reacting a corresponding benzaldehyde with

N-tert-butylhydroxylamine is new.

DETAILED DESCRIPTION - A process for the preparation of alpha -(2-4-disulfophenyl)-N-tert-butylnitrone compounds of formula (I) and their salts is new:

R = SO3H or a salt

Comprising reaction of an aldehyde of formula (II):

with freshly prepared N-tert-butylhydroxylamine (III):

(CH3)3CNHOH (III).

An INDEPENDENT CLAIM is also included for an integrated process for the preparation of a compound of formula (I) comprises:

(a) neutralizing (III) addition salt in an organic reaction medium to yield a solution of compound (III) free base;

(b) admixing (III) free base with an aldehyde of formula (II), thereby forming a condensation product comprising compound (I); and

(c) isolating compound (I) from the condensation product.

ACTIVITY - Cerebroprotective; Neuroprotective; Cytostatic; Vulnerary.

MECHANISM OF ACTION - None given.

USE - The compound alpha -(2,4-disulfophenyl)-N-tert-butylnitrone (Ia) can be used in the treatment of stroke and progressive central nervous system function loss conditions (see US5475032). It can also be used for ameliorating the side effects caused by **oxidative damage** resulting from Antineoplastic disease treatment (see US5508305) and concussion (see US780510).

ADVANTAGE - The method can provide high conversion rates and purity and is particularly suited to large scale production.

Dwg.0/0

L117 ANSWER 23 OF 23 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-514430 [56] WPIDS
DOC. NO. CPI: C2001-153700
TITLE: Production of N-tert-butyl-phenylnitrones, by reaction of benzaldehydes with N-**tertbutylhydroxylamine** salt, used in treatment of stroke, concussion, and disorders causing progressive loss of CNS function.
DERWENT CLASS: B05
INVENTOR(S): BLIXT, J; KRUK, H; MCGINLEY, J; POUHOV, S; VAJDA, J
PATENT ASSIGNEE(S): (ASTR) ASTRAZENECA AB; (CENT-N) CENTAUR PHARM INC; (CENT-N) CENTAUR PHARM; (BLIX-I) BLIXT J; (KRUK-I) KRUK H; (MCGI-I) MCGINLEY J; (POUH-I) POUHOV S; (VAJD-I) VAJDA J
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001051460	A1	20010719	(200156)*	EN	18
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001027203	A	20010724	(200166)		
US 2002128318	A1	20020912	(200262)		
BR 2001007483	A	20020903	(200264)		
NO 2002003316	A	20020709	(200273)		
US 6479697	B2	20021112	(200278)		
EP 1265856	A1	20021218	(200301)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
CZ 2002002383	A3	20021211	(200309)		
SK 2002000993	A3	20030304	(200321)		
KR 2002091077	A	20021205	(200324)		

HU 2002004111 A2 20030328 (200333)
CN 1395559 A 20030205 (200334)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001051460	A1	WO 2001-SE7	20010104
AU 2001027203	A	AU 2001-27203	20010104
US 2002128318	A1	WO 2001-SE7	20010104
		US 2001-806832	20010405
BR 2001007483	A	BR 2001-7483	20010104
		WO 2001-SE7	20010104
NO 2002003316	A	WO 2001-SE7	20010104
		NO 2002-3316	20020709
US 6479697	B2	WO 2001-SE7	20010104
		US 2001-806832	20010405
EP 1265856	A1	EP 2001-901619	20010104
		WO 2001-SE7	20010104
CZ 2002002383	A3	WO 2001-SE7	20010104
		CZ 2002-2383	20010104
SK 2002000993	A3	WO 2001-SE7	20010104
		SK 2002-993	20010104
KR 2002091077	A	KR 2002-708862	20020709
HU 2002004111	A2	WO 2001-SE7	20010104
		HU 2002-4111	20010104
CN 1395559	A	CN 2001-803584	20010104

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001027203	A	Based on	WO 200151460
BR 2001007483	A	Based on	WO 200151460
US 6479697	B2	Based on	WO 200151460
EP 1265856	A1	Based on	WO 200151460
CZ 2002002383	A3	Based on	WO 200151460
SK 2002000993	A3	Based on	WO 200151460
HU 2002004111	A2	Based on	WO 200151460

PRIORITY APPLN. INFO: SE 2000-55 20000110

AB WO 200151460 A UPAB: 20021031
NOVELTY - Production of N-tert-butyl-phenylnitrones (I), by reaction of benzaldehydes (II) with N-**tertbutylhydroxylamine** acetate (III) in a solvent is new.

DETAILED DESCRIPTION - Production of N-tert-butyl-phenylnitrones of formula (I) or their salts, by reaction of benzaldehydes of formula (II) with N-**tertbutylhydroxylamine** acetate (CH3)3CNHOH (III) in a solvent, is new:

R = SO3H or its salt.

ACTIVITY - Cerebroprotective.

MECHANISM OF ACTION - None given.

USE - (I) is used in treatment of stroke, concussion, and disorders causing progressive loss of CNS function.

ADVANTAGE - The process provides a simple route to (I) in high yield and purity from readily available reagents, and is easily adaptable to large scale production. The process is superior to prior art using the free base of N-**tertbutylhydroxylamine** acetate (III), which is unstable, must be freshly prepared, and turns blue on exposure to the air. The hydrochloride salt of (III) is inert. (I) also reduces the side effects caused by **oxidative damage** due to antineoplastic treatment.

Dwg.0/0

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